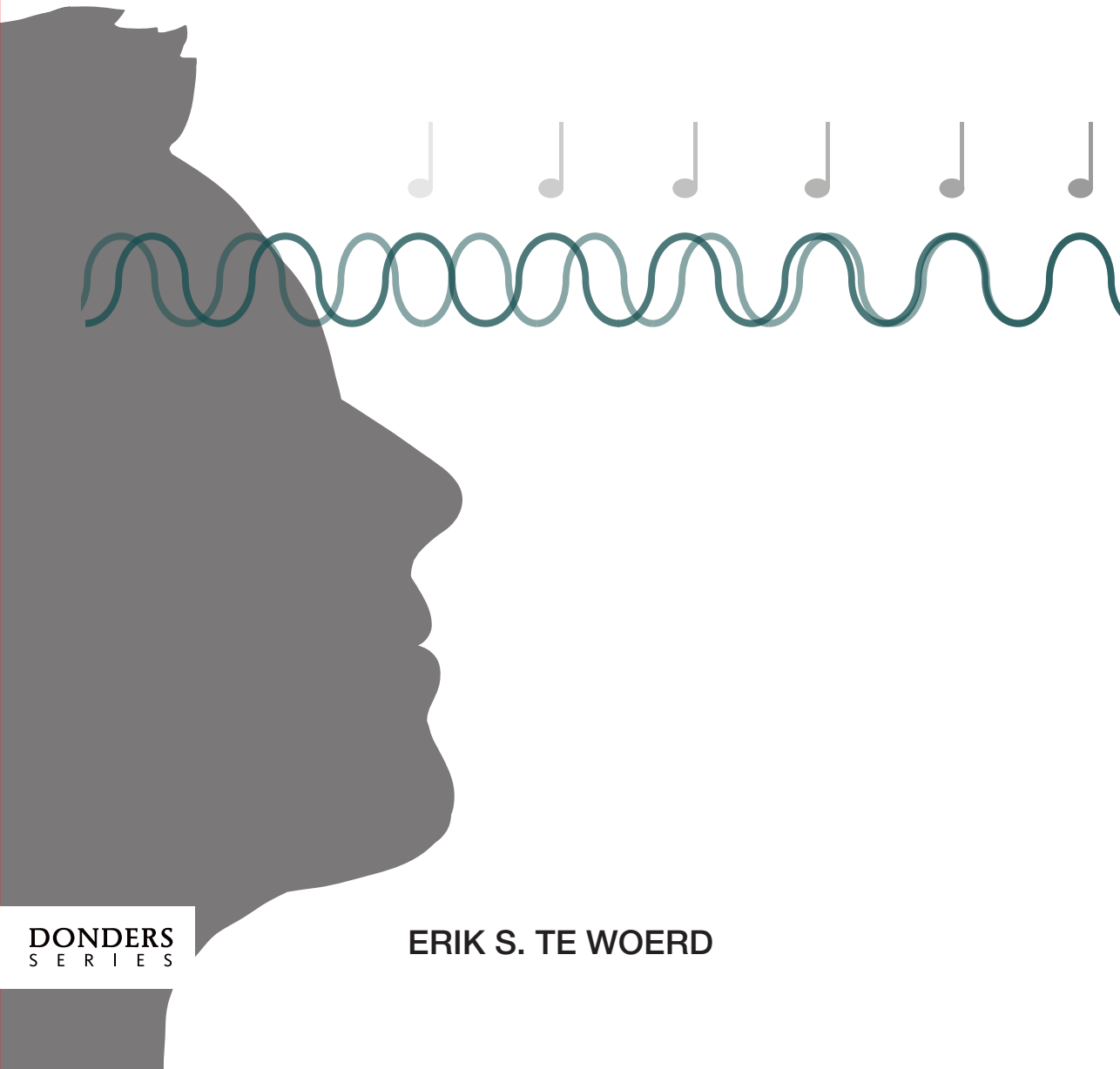
FEELING THE BEAT

THE NEUROPHYSIOLOGY OF CUEING IN PARKINSON'S DISEASE



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ERIK S. TE WOERD

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Erik S. te Woerd

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And those who were seen dancing
were thought to be insane by those
who could not hear the music

- Henri-Louis Bergson

Contents

General introduction and outline of thesis

1

The start of a new day is marked by sunrise and birds that start to sing their songs. We wake up, get ready, go to work, have dinner and go to sleep again. A sequence of events and activities forming the rhythm of our daily life. Not only do we find rhythm in our daily activities, rhythms can also be found on much longer time scales, such as the changing of seasons or the yearly rotation of our planet around the sun, and on shorter time scales such as tidal changes, music, and our very own heart beats. With such abundance of rhythm in our environment, it should come as no surprise that our brain is well-equipped to deal with these temporal regularities. Moreover, the brain can produce a range of rhythms such that we can align our bodily movements with the environment. A convincing example is the fact that we have all experienced the strong feeling that you want to dance when hearing music, or even more remarkable, that you are moving to the beat and only become aware of this when the music stops. Neurological disorders such as Parkinson's disease (PD) can disrupt the production of rhythms in the brain, leading to problems with movements such as gait. Numerous scientific studies have shown that gait deficits in PD patients can be ameliorated with the use of rhythmic stimuli, commonly referred to as rhythmic cueing. While the beneficial behavioural effects of such cueing techniques have become clear, the neurophysiology underlying these positive effects is not. Presumably, the efficacy of cueing depends on the entrainment of motor responses. Accordingly, neural correlates of entrainment, in the form of motor preparatory electrical potentials, have been shown to automatically adjust to external regularities. However, this is not the case in PD patients. Moreover, there is evidence that patients are impaired in the perception of beat-based rhythms, i.e. precisely the rhythms that tend to engage the motor system. This reveals an apparent paradox: if PD patients are insensitive to temporal regularities and impaired in beat perception, then how does rhythmic cueing improve their motor function? Almost serendipitously, there has been a surge of interest in slow brain oscillations and the entrainment of such oscillations by environmental rhythms. Entrained oscillations adjust their phase and frequency to the inherent rhythm of a task and thereby optimize processing in relevant brain areas. This new framework provides an oscillatory perspective that may help resolve the paradox of rhythmic cueing just outlined. In this thesis, I will therefore investigate the neurophysiology underlying the effects of cueing, and the role of prediction and attention in this process, from an oscillatory perspective, aiming to provide more insight into how external rhythms can improve motor function.

1.1 Rhythmic cueing

Cueing improves gait in patients with PD

One of the most disabling features of Parkinson's disease (PD; see BOX 1) is its negative impact on gait (Boonstra et al., 2008; Meara and Koller, 2000). PD leads to instability of gait, but also causes problems in the pattern of gait characterized by faster cadence, reduced stride length, reduced velocity and an increased variability in the stride-to-stride gait cycle timing (Hausdorff et al., 1998; Knutsson, 1972; Morris et al., 1996b; Rogers, 1996). The impaired gait can also lead to "freezing", where patients are unable to initiate an effective forward step; patients have the feeling that one or both feet are "glued" to the floor. Freezing of gait is often associated with an increased risk of falls, which can have severe consequences for the patients' quality of life and even their survival, among others due to fall-related major injuries (for review see Bloem et al., 2004). Fortunately, many of the motor symptoms of PD can be ameliorated with levodopa, a precursor of dopamine, or with dopamine agonists, but the efficacy of dopaminergic medication on gait-related motor symptoms is limited (Marsden and Parkes, 1977; Thanvi and Lo, 2004). Despite the positive effects of dopaminergic medication on motor functioning, gait deficits and postural instability are only partially responsive to medication (McNeely et al., 2012), and some problems may even get worse following dopaminergic medication (Espay et al., 2012). The insufficient effect of medication on gait, and taking into account that this effect even diminishes over time due to the progressive nature of PD, has initiated studies into alternative ways to improve gait in PD, such as physical therapy (Keus et al., 2014; Morris et al., 2010; Rubinstein et al., 2002). In this field, it is well known that the use of rhythmic stimuli ("cueing") can facilitate gait in patients with PD (Martin, 1967; Von Wilzenben, 1942), and these early observations have now been confirmed by high-quality clinical trials (Nieuwboer et al., 2007).

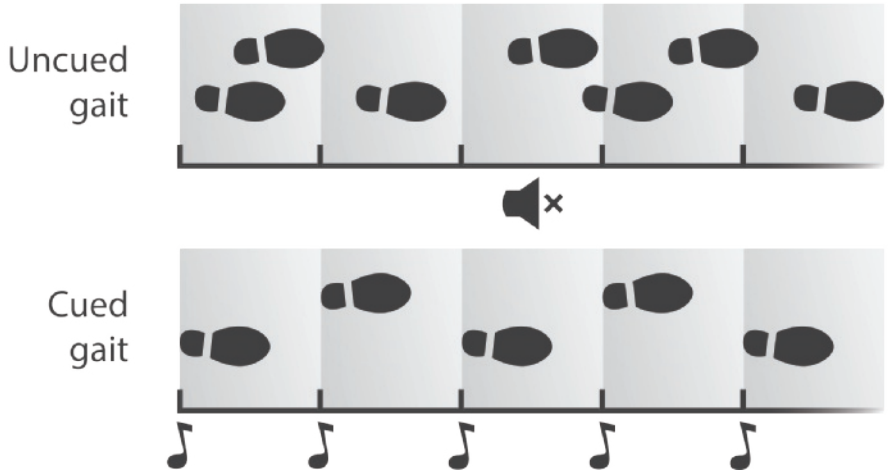

Figure 1.1 Schematic illustration of parkinsonian gait with and without cueing. Top: self-paced gait of a patient with Parkinson's disease shows high variability in stride length. Bottom: gait of a PD patient when rhythmic auditory cues are used to pace gait shows much more regular stride length.

Cueing can either be discrete or rhythmic, where either a single stimulus is presented to initiate gait (e.g. a single stripe pasted onto the floor) or several stimuli are presented in a rhythmic fashion to pace gait, respectively. Throughout this thesis, the main focus is on rhythmic cueing, so wherever 'cueing' is used here this refers to rhythmic cueing. Cueing can be used with auditory, visual or somatosensory stimuli and has an almost immediate positive effect on gait (for reviews see Ashoori et al., 2015; de Dreu et al., 2012; Lim et al., 2005; Nombela et al., 2013; Rubinstein et al., 2002; Spaulding et al., 2013). The aforementioned reviews all show positive effects on gait, among which improvements in gait cadence, stride length, velocity and postural stability (see Figure 1.1).

BOX 1: Parkinson's disease (PD)

Parkinson's disease (PD), first described by James Parkinson in 1817 in his "Essay on the Shaking Palsy", is the second most common neurodegenerative disorder (Hirtz et al., 2007). PD is a progressive disease and has a mean onset age of 55 years, and the incidence increases with age. PD can also appear in much younger patients and is then defined as young-onset PD (Bhidayasiri and Tarsy, 2012). In most cases (75-90%) the cause of the disease is unknown and termed "idiopathic" PD (Hughes et al., 1992). Several hypotheses have been put forward about risk factors, which vary from genetic factors to exposure to pesticides in the environment (for an extensive review on risk factors see De Lau and Breteler, 2006). The pathological hallmark of PD is a loss or degeneration of dopaminergic cells in the substantia nigra pars compacta (SNpc), and development of Lewy Bodies in dopaminergic neurons (for review see Dauer and Przedborski, 2003). At the time when symptoms occur, the level of dopamine in the putamen has dropped by 80%, and about 60% of the dopaminergic neurons in the SNpc have disappeared (Fearnley and Lees, 1991).

The most striking and well-known symptoms of PD are those in the motor domain, the cardinal features being rigidity, absence of movement (akinesia) or slowness of movement (bradykinesia), tremor and postural instability (Jankovic, 2008). Tremor in PD is mostly observed during rest and decreases with voluntary movement (for a review on tremor pathophysiology see Helmich et al., 2013). Bradykinesia and akinesia are manifested in a variety of ways, such as a loss of normal facial expression, reduced voice volume and decreased size and speed of handwriting (Berardelli et al., 2001). In addition to these symptoms, patients often develop problems with gait, mostly presented as short shuffling steps, and they develop a stooped posture.

Besides these motor symptoms, PD can also lead to important non-motor symptoms including cognitive changes and dementia, behavioural / neuropsychiatric changes, autonomic nervous system failure, and sleep disturbances (Dauer and Przedborski, 2003; Jankovic, 2008; Lim and Lang, 2010). Other neurobehavioural abnormalities seen in PD are features of obsessive-compulsive and impulsive disorder, like craving, binge eating, pathological gambling and compulsive shopping (most of these are related to adverse effects of the dopaminergic medication). Finally, PD can lead to sensory abnormalities ranging from olfactory dysfunction to pain (Beiske et al., 2009; Djaldetti et al., 2004; Stern et al., 1994).

Presumed physiological basis of cueing

Since numerous studies have shown positive effects of cueing in PD patients, several suggestions regarding the physiological basis underlying these effects have been put forward. One of the most important views states that external cues enable movement on the basis of a recruitment of lateral premotor areas, probably supported by greater reliance on cerebellar-thalamocortical circuits, effectively bypassing deficient basal ganglia-medial premotor circuits in PD (Benoit et al., 2014; Cunnington et al., 1995, 2001; Heremans et al., 2012; Rochester et al., 2007; Samuel et al., 1997; Sen et al., 2010; Vercruysse et al., 2012; Yu et al., 2007). This view claims support from neurophysiological studies in primates that show a preferential involvement of the medial premotor cortex in self-initiated movements and of the lateral premotor cortex in externally cued movements (Mushiake et al., 1991), and from neuroanatomical work identifying the medial premotor cortex (as opposed to the lateral premotor cortex) as key projection area of basal ganglia output (Schell and Strick, 1984).

This view on cueing, assuming a shift in activation from medial to lateral premotor cortex and, subcortically, a shift from basal ganglia to cerebellum (Yu et al., 2007; see Figure 1.2), has also been criticized, however. It is no longer believed that basal ganglia output to motor areas excludes the lateral premotor cortex (Hoover and Strick, 1993). Likewise, it has been noted that there is no preferential involvement of the basal ganglia in internally generated movements (Ballanger et al., 2006; Turner and Anderson, 2005), and that functional specialization of medial and lateral premotor cortex for internally and externally cued movements is relative (Cunnington et al., 2002; Gowen and Miall, 2007; Jahanshahi et al., 1995; but see Debaere et al., 2003). Moreover, in a recent meta-analysis of imaging studies in PD, no evidence was found for a shift in activation from medial to lateral premotor areas (Herz et al., 2014a). Imaging studies comparing patients while either on or off medication, furthermore, have shown that relative overactivation of the lateral premotor cortex in PD is a feature of the off state only, being eliminated by dopaminergic therapy, which restores activity and connectivity of the supplementary motor area (SMA) (Michely et al., 2015; Rowe et al., 2010). Electroencephalographic (EEG) studies using this approach revealed a similar pattern in restored oscillatory

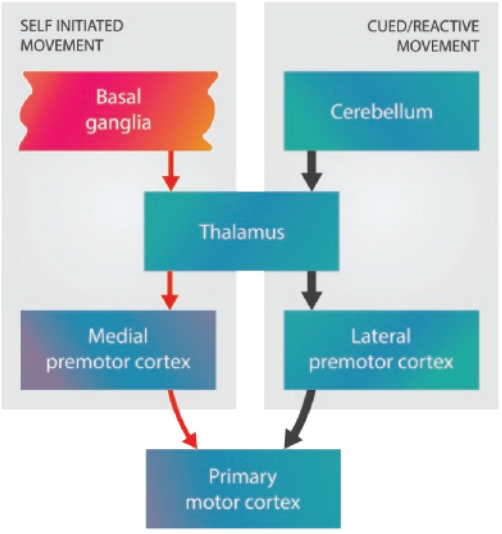

Figure 1.2 Schematic overview of current ideas about the neurophysiology of cueing. It is suggested that there are two separate circuits for movement: one for self-initiated movements and one for cued or reactive movements. Since Parkinson's disease affects the basal ganglia (highlighted in red here), this mainly affects self-initiated movements with relative sparing of externally cued movements.

coupling of the SMA with prefrontal, premotor and motor cortex (Herz et al., 2014b, 2014c). Finally, more recent work has shown that the SMA does not drive the execution of internally generated movements, but that this is performed by a large cortical and subcortical network, among which the SMA, premotor cortices, basal ganglia and cerebellum (Elsinger et al., 2006; Hoffstaedter et al., 2013; Vaillancourt et al., 2003, 2007). In this network, the caudate has a role in selecting appropriate movement parameters such as the amount of force, while the putamen is particularly important for the timing of movement (for an extensive review see Hackney et al., 2015). In sum, it appears that the suggestion of a strong distinction between internally generated (processed by the medial premotor cortex) and externally cued movements (processed by the lateral premotor cortex) is not so clear after all, and that longstanding views on the neurophysiology of cueing have insufficient empirical support.

Even though the outlined theoretical basis of cueing seems now outdated, cueing may nonetheless be effective. However, other recent work poses new challenges to the concept of cueing, which makes it mandatory to re-examine its physiological basis. First, mere listening to rhythms with a regular beat structure does produce activation in motor structures such as the basal ganglia, lateral and medial premotor cortex (Chen et al., 2008; Grahn and Rowe, 2009; Teki et al., 2011), but PD patients are specifically impaired in the perception of such beat-based rhythms (Grahn and Brett, 2009). Second, in healthy controls, movement preparatory EEG-potentials become synchronized to temporally predictable external events even when this is detrimental (Breska and Deouell, 2014), and are generated by the lateral premotor cortex (Praamstra et al., 2006), but PD patients do not show this entrainment (Praamstra and Pope, 2007). These results suggest that (i) cueing does not produce motor activation that bypasses the basal ganglia; (ii) cueing invokes a predictive instead of a reactive mode of activation; and (iii) cueing depends on basal ganglia-cortical circuits involving the lateral premotor cortex. These circuits are affected in PD and may therefore not sustain the automatic entrainment of motor responses normally afforded by cueing. Note that these points do not imply that cueing does not or cannot work (see the considerable supporting evidence for cueing in the previous paragraph), but they do indicate that cueing is more complex than previously thought or may have more restricted application.

1.2 Behavioural entrainment

The use of rhythmic cueing in PD might be seen as motor entrainment, where entrainment is defined as the synchronization of human movement with the rhythm of an external stimulus, as in dancing (see Figure 1.3) (Large and Palmer, 2002; for review see Repp, 2005; Repp and Su, 2013). Entrainment depends on three critical components, namely (i) the ability to perceive rhythmic signals, (ii) the ability to produce rhythmic signals, and (iii) the ability to integrate sensory information and motor production thereby enabling adjustment of motor output based on rhythmic sensory input (Phillips-Silver et al., 2010).

Figure 1.3 One of the most extreme examples of behavioural entrainment is shown by dance groups, where each dancer synchronizes his/her bodily movements to the rhythm of the music and to all other dancers. This synchronization requires not only the capacity to perceive rhythm (dancers must hear the music and watch the other dancers), but also the ability to produce rhythm (move to the beat) and the ability to integrate these systems to synchronize movement to the rhythm (if one perceives he/she is moving too fast then movements should be slowed down to synchronize again).

The environment is full of information that has a rhythmic structure, such as footsteps, the diurnal cycle, and music. Organisms synchronize their own biological rhythms to these and other cyclical processes (Foster and Kreitzman, 2005), probably because this synchronization provides evolutionary advantages. Humans do not need training to perceive these rhythms, and therefore it appears that rhythm perception is a robust and innate behaviour, as it can even be seen in newborns (Honing et al., 2009; Phillips-Silver and Trainor, 2005; Winkler et al., 2009). Producing rhythmic output is another requirement for entrainment, and the capacity to do so may also have developed because of evolutionary advantages such as in mating (Greenfield, 1994). This view agrees with Darwin's ideas about the evolution of human musicality (Patel, 2014), which he believed to have deep evolutionary roots, posing that 'The perception, if not the enjoyment, of musical cadences and of rhythm is probably common to all animals, and no doubt depends on the common physiological nature of their nervous systems' (Darwin, 1871). Finally, in order to be able to entrain to an external rhythmic signal, one needs to integrate the systems of rhythm perception and rhythm production, as this allows the internally produced rhythm to be adjusted in such a way that it aligns with the perceived external rhythmic signal (Phillips-Silver et al., 2010).

For a long time, it was thought that the skill of or susceptibility to entrainment was unique in humans. When you think about it, this seems natural as even animals that have been domesticated do not synchronize to a beat. Put simply: 'why don't dogs dance?' (Fitch, 2012). An explanation for this is the fact that beat perception requires several brain structures and functions to be present, and among the most important structures are the basal ganglia (Grahn, 2009; for review see Merchant et al., 2015). The basal ganglia are not only important for rhythm perception, but also have a major role in interval timing (Teki et al., 2012; for review see Coull et al., 2011), motor control and sequencing (Aldridge et al., 2004; Bhutani et al., 2013; Brown and Marsden, 1998; Graybiel, 1995). These findings point to an important

role of the basal ganglia in the integration of rhythm perception and production systems, allowing an organism to synchronize movement to an external rhythm. However, if the basal ganglia were the only requirement for behavioural entrainment, countless other animals would also show this behaviour because the basal ganglia have a role in perceptual timing and motor control in a range of species (for review see Buhusi and Meck, 2005). Together with the finding that rhythm perception is stronger in the auditory than the visual domain (Hove et al., 2013; Repp and Penel, 2002), this has led to the "vocal learning and rhythmic synchronization hypothesis" (Patel, 2006).

This vocal learning hypothesis suggests that in human evolution, vocal learning modified the basal ganglia in such a way that a strong coupling between auditory input and motor output was created, and that this coupling is a critical component for behavioural entrainment. This view is supported by a video-analysis of entrainment among many different animals (Schachner et al., 2009), but data from that study also show that vocal learning alone is not sufficient for entrainment (Fitch, 2009). This latter point is incorporated in the "Gradual audio-motor hypothesis", which views behavioural entrainment as a byproduct that was created during the evolution of the motor system (for review see Mendoza and Merchant, 2014). This theory suggests that the complex entrainment capacities of humans have developed across primates in a gradual fashion, with duration-based timing mechanisms present in all primates, but a beat-based timing mechanism that is most developed in humans, least developed in monkeys, and of an intermediate level in chimpanzees (which are closer to humans on the evolutionary scale than monkeys). More detailed information on these different timing systems will follow in a later section of this Introduction. Additional evidence for the Gradual audio-motor hypothesis comes from studies that have shown that macaques do have the capacity for period matching (Merchant et al., 2011; Zarco et al., 2009), but lack the skill for phase correction (Zarco et al., 2009). These are two crucial components in behavioural entrainment, where period matching refers to the fact that the period of movement precisely equals the beat period, and phase matching means that the movement occurs close to or at the onset time of the beat. That is, one can have perfect period matching but move in anti-phase with the beat. Therefore, while period matching is important, one also needs to be able to adjust the phase of movement such that each movement aligns with the onset of the beat, showing that both components are crucial for accurate entrainment. In the case of monkeys, it was shown that they do not show full phase correction, but that their tapping time is shorter than their standard reaction time. This suggests that monkeys do have some capacity for phase matching, only not as strongly developed as in humans (Merchant and Honing, 2014; Patel, 2014).

Accurate entrainment requires precise temporal adaptation (reactive error correction) and anticipation (predictive processes) (Repp and Su, 2013). Without reactive correction of timing errors, variability would increase over time and result in asynchronies (timing error between occurrence of the action and the external event), phase drift and the loss of synchronization (Vorberg and Wing, 1996). Anticipating the onset of the external event is equally important for behavioural entrainment, as this process allows an action to start early enough and coincide with the external

event. In order to do so, the brain has evolved the capacity to generate temporal predictions about the near future (Schubotz, 2007). A well-known phenomenon in entrainment-studies that supports this anticipatory nature is the negative mean asynchrony that is typically seen in tapping tasks. This means that the finger taps of participants often occur a bit earlier than the onset of the external stimulus (for reviews see Repp, 2005; Repp and Su, 2013). To explain these processes underlying behavioural entrainment or sensorimotor synchronization, models such as the 'ADaptation and Anticipation Model' (ADAM) have been developed (Van der Steen and Keller, 2013).

Studies on behavioural entrainment also require investigation of the neural processes that underlie rhythmic movements and, interestingly, it has been shown that sensory stimuli that have a rhythmic structure are able to entrain oscillatory activity in the sensory cortices of macaques (Lakatos et al., 2008) and humans (Besle et al., 2011; Saleh et al., 2010). This entrainment extends beyond the sensory systems, and is also able to entrain oscillatory activity in the human motor system (Praamstra et al., 2006; Saleh et al., 2010). Evidence for entrainment of brain oscillations to rhythmic events provides a basis and neurophysiological explanation for earlier work showing that slow preparatory brain potentials automatically adjust to regularities in behavioural tasks (Praamstra et al., 2006). The phenomenon of entrainment of brain oscillations provides a novel perspective for the investigation of motor entrainment to an external rhythm and may provide better insight into the neurophysiology of cueing in PD. Our approach in this investigation of the physiology of cueing is therefore targeted at neurophysiological correlates of entrainment in the form of oscillatory activity as measured with magnetoencephalography (MEG) (see BOX 2).

BOX 2: Magnetoencephalography (MEG)

Weak electrical currents in the brain produce small magnetic fields. These small magnetic fields can be measured using an MEG scanner, containing highly sensitive measuring devices called SQUIDS (superconducting quantum interference devices). To be able to do this, the SQUIDS are positioned in a container with liquid helium, cooling them to approximately 4 degrees Kelvin. At this very low temperature, the sensors become superconducting and are able to measure the weak magnetic fields produced by the brain. To avoid strong noise influences of magnetic fields coming from the environment, the MEG is located inside a magnetically shielded room.

In order for the brain magnetic fields to be measurable outside of the skull, a population of neurons should be active in a coordinated way in time and spatially organized, such that their signals sum up to a measurable signal (Lopes da Silva, 2013). Pyramidal neurons in the cortex have this feature of spatial alignment, and their intra- and extracellular currents are assumed to be the main contributors to the MEG signal (Ioannidis, 2006).

The main advantage of MEG compared to the more common and cheaper EEG, is the higher spatial resolution of MEG. This is due to the fact that the magnetic fields produced by the brain pass the skull without distortion, while the electrical currents (which are recorded in EEG) that underlie these magnetic fields are strongly smeared out over the skull due to the skull's poor electrical conductance.

1.3 Neural oscillations

In order to move in time with a perceived rhythmic stimulus, the brain must extract the temporal regularity in the incoming information and predict when the next beat will occur. Recent studies have shown that predictive timing involves a network of sensory and motor structures, and it is suggested that processing within and interactions between these systems are accomplished via neural oscillations in different frequency bands (Arnal, 2012; Fujioka et al., 2009, 2012; Lakatos et al., 2008). This oscillatory brain activity, first discovered in the EEG by Berger (1929), is found throughout the brain and has been implicated in numerous physiological processes. In general, oscillatory brain activity is divided in five frequency bands: delta (1 - 4 Hz), theta (4 - 8 Hz), alpha (8 - 12 Hz), beta (13 - 30 Hz; although there are also studies making a further division into a low (12-20 Hz) and high (20-30 Hz) beta-band (e.g. Lopez-Azcarate et al., 2010; Roopun et al., 2008)) and the gamma (> 30 Hz) frequency range. It was suggested long ago that oscillations reflect cyclical variations in excitability of neuronal tissue (Bishop, 1932), a proposition that was later supported by work of others (Lakatos et al., 2005). Two frequency bands, the delta and beta-band, are of main interest in this thesis and in the following sections I will more extensively introduce them and explain why they are so relevant to the topic at hand.

BOX 3: Attention and prediction

Attention can be described as a two-way process, where on the one hand, the focus of attention can be influenced in a bottom-up manner in which attention is oriented towards salient stimuli from the environment (exogenous attention). On the other hand, attention can be implemented in a top-down fashion, where attention is voluntarily oriented towards relevant objects, controlled by cognitive factors such as knowledge and current goals (endogenous attention), thereby selecting behaviourally relevant sensory input for further processing, and suppressing all other input (for reviews see Corbetta and Shulman, 2002; Ruff, 2013).

Both types of attention are processed by a network of frontal and parietal areas, but whereas top-down attention arises from frontal cortex, bottom-up attention is driven by sensory areas. Additionally, the frequency at which oscillatory synchrony between frontal and parietal cortices takes place depends on the type of attention being employed (Buschman and Miller, 2007).

Prediction is the process of using experiences and statistical regularities from the past, to predict when something, as in temporal predictions, or what, is going to happen in the (near) future. The origin of temporal predictions is thought to be in motor areas of the brain (for review see Morillon and Schroeder, 2015).

Delta-band oscillations

Neural oscillations in the delta frequency band or slow oscillations in general, were always suggested to be seen only in the sleeping brain (Achermann and Borbély, 1997; Steriade, 2006), and would disappear during awakening (Steriade et al., 1993). However, recent work has radically changed this view and showed an important role for delta oscillations in several cognitive functions, ranging from motivational processes to modulating the activity in neuronal networks (for reviews see (Harmony, 2013; Knyazev, 2012).

Although earlier work shows that attention leads to increased gamma oscillations and a suppression of slow delta oscillations (Fries et al., 2001), it was proposed more recently that delta oscillations actually do have an important role in attentional selection (Schroeder and Lakatos, 2009). This proposition suggests that the brain operates either in a 'continuous' or 'rhythmic' processing mode, depending on the dynamics of the task. In situations where it is uncertain when behaviourally relevant stimuli will show up, slow oscillations are suppressed to keep a continuous level of high excitability and thereby enable fast responses to each presented stimulus (Lakatos et al., 2008). However, when stimuli possess a certain temporal regularity, the brain can use temporal prediction to allocate attention only to those relevant moments in time (see BOX 3). This rhythmic-mode processing would then entail sensory entrainment to the temporal structure of the attended stream, thereby aligning the high-excitability phase of the delta oscillations with the events in this attended stimulus stream. This phase-alignment of delta oscillations functions as a temporal filter, leading to a systematic enhancement of responses to the attended events and a suppression of responses to events that occur out of phase with the attended events (Lakatos et al., 2008, 2013a). The process of delta entrainment can thus be regarded as a physiological manifestation of the "Dynamic Attending Theory" (Herrmann and Henry, 2014; Large and Jones, 1999). This theory describes attention as the behaviour of internal oscillations, termed attending rhythms, that can entrain to (rhythmic) external events and focus attentional energy to relevant points in time. Several studies have supported this proposition, by showing entrainment of delta oscillations along with temporal predictions (Wilsch et al., 2015), and subsequent positive behavioural effects such as increased contrast sensitivity (Cravo et al., 2013), improved auditory perception (Henry et al., 2014; Henry and Obleser, 2012), and faster response times (Cravo et al., 2013; Lakatos et al., 2008; Stefanics et al., 2010).

In addition to the important role in attention and prediction, the frequency range of delta oscillations coincides with the optimal range for perception of music tempos (1-3 Hz) (Large, 2008). In sum, the functional role of delta oscillations in attention, temporal prediction and rhythm processing makes slow oscillations an important neural correlate in the investigation of the neurophysiology of rhythmic cueing in PD.

Beta-band oscillations

Beta-band oscillations were always regarded a rhythm that is particularly important in the motor system, given that these oscillations are well represented in motor areas and occur throughout the entire motor system (Brown, 2007). Oscillatory activity in the beta-band was long considered to reflect an idling state of the motor cortex (Pfurtscheller et al., 1996), since beta oscillations are most pronounced during rest and steady contractions. Studies investigating beta-band oscillations during movement have shown that beta oscillations are suppressed shortly before and during movement, followed by an overshoot (the beta-rebound) once the movement is terminated (for review see Kilavik et al., 2013). Interestingly, beta-band oscillations are also suppressed when one is imagining a movement (Brinkman et al., 2014; de Lange et al., 2008). Beta-band oscillations are not only modulated during movement, but also undergo changes in anticipation of a movement, reflecting anticipatory processes. Indeed, it was shown that beta-band activity is modulated in premotor and motor cortices even seconds before a movement is made (Donner et al., 2009), and that beta power increases prior to an expected postural challenge (Androulidakis et al., 2007a).

Recent studies have therefore proposed a functional role for beta oscillations in which beta oscillations are a signature of an active process that promotes the existing motor set over the processing of new movements (Androulidakis et al., 2007a; Gilbertson et al., 2005). Similarly, Engel and Fries (2010) have suggested that periods of high beta power serve to maintain the current sensorimotor or cognitive state (i.e. the 'status quo'), whereas periods with low beta power provide the flexibility to change this state. In this theory, the idea is that beta-band power (or coupling in beta-band frequencies) is expressed stronger if the maintenance of the status quo is predicted or intended, and that beta-band power is lowered if the current motor or cognitive set has to be changed. This 'set' reflects the fact that humans respond faster to a stimulus when the movement to be made is known in advance (motor set), or that humans are faster at detecting objects when features of that object are known (perceptual set) (for review see Corbetta and Shulman, 2002).

Beta-band oscillations are not only important in the motor system but have a functional role in numerous other brain areas and cognitive processes. For example, beta oscillations are implicated in auditory attention and prediction (Todorovic et al., 2015), and in mediating auditory-motor coupling (Fujioka et al., 2012). Moreover, beta oscillations have been implicated in timing processes (Arnal, 2012; Arnal et al., 2015; Cirelli et al., 2014; Fujioka et al., 2012; Kononowicz and van Rijn, 2015; but see Meijer et al., 2016). For example, Iversen et al. (2009) showed that beta, but not gamma, oscillations evoked by tones in a repeating pattern were affected by whether or not listeners imagined them as being on strong or weak beats. Of special importance in the present context are the findings that beta oscillations are crucial for predictive timing in auditory beat processing and that beta oscillations involve interactions between auditory and motor regions (Fujioka et al., 2009, 2012)

Another aspect that makes beta oscillations very relevant in our investigation of the neurophysiology of rhythmic cueing in PD, is that PD is well known to be accompanied

by an excess of oscillatory synchrony in the beta band (for reviews see Boraud et al., 2005; Hammond et al., 2007). This holds true for local field potentials in the basal ganglia and, less frequently observed, cortical beta oscillations measured by means of EEG or MEG (Crowell et al., 2012; Pollok et al., 2012). The origin of this increase in oscillatory beta band power is unknown, but studies have suggested that it may be due to inhibitory interactions between striatal medium spiny neurons (McCarthy et al., 2011), due to intrinsic rhythmic firing in the network between the subthalamic nucleus (STN) and the external segment of the globus pallidus (Gpe) (Bevan et al., 2002), or a delayed consequence of chronic dopamine depletion (Mallet et al., 2008). Excessive synchronization of beta oscillations reduces the information coding capacity of affected neuronal ensembles (for review see Hanslmayr et al., 2012), which may contribute to parkinsonian motor impairment (Brittain and Brown, 2014). In terms of the aforementioned 'status-quo signalling': the abnormally strong beta-band power in PD patients leads to an abnormal persistence of the status quo and deterioration of flexible behavioural and cognitive control (Engel and Fries, 2010). Correlations between clinical improvement and attenuation of STN beta power by dopaminergic medication and/or deep brain stimulation of the STN (Giannicola et al., 2010; Kühn et al., 2006, 2008, 2009; Ray et al., 2008), have supported the notion that high beta power may contribute to parkinsonian bradykinesia and rigidity. The possibility of a causal rather than epiphenomenal relation is supported by evidence at both the cortical and subcortical level. That is, it has been shown that increasing cortical beta-band power by means of transcranial alternating current stimulation slows down movement (Joundi et al., 2012; Pogosyan et al., 2009). Similar findings have been obtained at the subcortical level, using deep brain stimulation, showing this effect to be frequency-specific to the beta-band (Chen et al., 2007). The similar effect of beta-band stimulation at the subcortical and cortical level suggests that there are at least some similarities in the functional role of beta oscillations at these different levels. However, it remains unclear to what extent cortical beta oscillations reflect basal ganglia beta activity, since basal ganglia oscillations predict only about 20% of the cortical beta activity (Lalo et al., 2008; Litvak et al., 2011).

The theory on 'status quo-signalling' was later refined and placed in the context of dopamine function by Jenkinson and Brown (2011). They proposed that beta activity in the basal ganglia-cortical system provides an internal likelihood index of the need for a novel voluntary response (Jenkinson and Brown, 2011). Furthermore, this index is suggested to be a direct consequence of net dopamine levels at sites of cortical input into the basal ganglia. Within the basal ganglia-cortical system, the level of beta power is then inversely related to the likelihood of a new voluntary action, enabling anticipatory resourcing based on the extent to which internal and external cues predict the need for action (Jenkinson and Brown, 2011). In short, this means that beta activity, and specifically its predictive suppression, determines motor readiness.

Oscillatory entrainment

One way of studying brain function is to present an external stimulus and measuring how the brain responds to this stimulus. This approach assumes that neurons simply respond in a reflexive manner, and that background neural activity is noise (Raichle, 2010). Many studies have shown that neurons do not always respond in the same way to the same stimulus, as the neuronal response is influenced by processes such as prediction, attention and prior states (Paris et al., 2016; for review see Gilbert and Sigman, 2007). Besides these factors, it is known that ongoing oscillatory activity, reflecting neural excitability, can modulate responses to stimuli in sensory areas and influence motor processing (Buzsáki, 2006; Thut et al., 2012; for review see Sadaghiani et al., 2010). Importantly, presentation of rhythmic stimuli, as in cueing, has been shown to entrain not only behavioural responses but also ongoing oscillatory activity. This oscillatory entrainment aligns periods of high neural excitability with time points at which subsequent stimuli are expected (Lakatos et al., 2008, 2013a). Entrainment of ongoing oscillations is most likely accomplished via a phase reset of these oscillations by incoming stimuli (Lakatos et al., 2013a). In an experimental context, phase resetting can be induced by transcranial magnetic stimulation (for review see Thut et al., 2011). Entrainment effects have been shown in different frequency-bands, with studies showing entrainment of delta (Cravo et al., 2013; Lakatos et al., 2008; Saleh et al., 2010), alpha (Rohenkohl and Nobre, 2011; Spaak et al., 2014) and beta (Fujioka et al., 2012; Lakatos et al., 2013b; Miller et al., 2012) oscillations.

The alignment of high excitability phases with the timing of rhythmic external stimuli, during entrainment, leads to a systematic enhancement of neural responses to these stimuli (Lakatos et al., 2005; see Figure 1.4). Additionally, stimuli that are presented in-between two behaviourally relevant stimuli arrive during a phase of low neuronal excitability and are suppressed. Therefore, entrainment has been suggested to underlie selective attention in situations where there is more than one (rhythmic) stimulus stream to attend, by acting as a temporal filter (Denison et al., 2017; Lakatos et al., 2013a; Schroeder and Lakatos, 2009). Studies have shown that entrained oscillations enhance and stabilize sensory representations of attended rhythmic stimuli (Cravo et al., 2013; Mathewson et al., 2010; Rohenkohl and Nobre, 2011), and are thought to have a broad role in temporal prediction (for review see Calderone et al., 2014). However, when there is no temporal predictability in the external input, slow oscillations are suppressed and the brain uses a 'vigilance mode' in which there is a more continuous sampling of input (Schroeder and Lakatos, 2009). On a side note, while the focus in this thesis is on rhythmic stimuli and entrainment, recent studies have shown that attention operates periodically, even in the absence of entrainment (Landau and Fries, 2012). It was shown, namely, that the performance in a change-detection task fluctuates at a theta and / or alpha rhythm (Busch et al., 2009; Landau and Fries, 2012), suggesting that attention oscillates in itself.

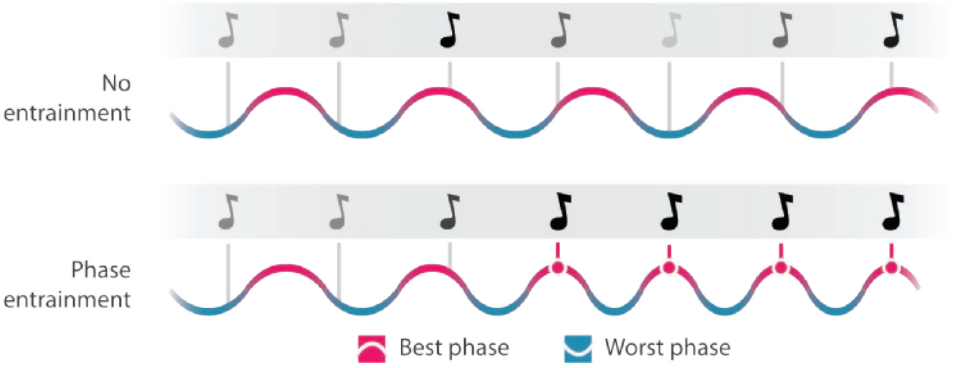

Figure 1.4 Schematic illustration of oscillatory entrainment and its consequences. Neural oscillations are believed to represent excitability of the underlying neural tissue. At the best phase (red) excitability is high and stimuli are processed faster and more accurate than at the worst phase (blue). Top: a neural oscillation that does not show entrainment to the external stimuli. Stimuli arrive at random phases of the neural oscillation and are processed with varying speed and accuracy (represented by the boldness of auditory stimuli; bolder is better). Bottom: a neural oscillation that entrains to the rhythm of the external stimuli. This entrainment causes the ideal phase to align with the external stimuli such that these stimuli are always processed fast and accurately.

Oscillatory entrainment does not only occur in sensory areas, but has also been shown to occur in motor areas of the brain (Besle et al., 2011; Praamstra and Pope, 2007; Saleh et al., 2010; Stefanics et al., 2010). For example, delta oscillations were shown to entrain to external stimuli and the strength of entrainment was correlated with response time to target stimuli (Stefanics et al., 2010). Interestingly, the study of Saleh and colleagues (2010) used intracranial recordings in the primary motor cortex to show that oscillatory activity entrains only during behaviourally relevant stimuli. Moreover, entrainment does not only involve primary sensory and motor cortices (Besle et al., 2011), but occurs in a larger network that largely overlaps with the network used in temporal attention and prediction (Coull and Nobre, 1998; Nobre et al., 2007). These findings suggest that oscillatory entrainment can optimize processing not only in sensory, but also in motor areas, and could therefore play a role in the positive effects seen during rhythmic cueing in PD.

1.4 Timing

Given the important role of temporal regularities in rhythmic cueing and entrainment, it is important to address the question how time is represented in the brain. Early observations on the rhythmic physiology of human brain function led to the proposal that the nervous system has the capacity to represent time and may function as a clock (Gooddy, 1958). From there, many studies have been launched to investigate how time is represented in the brain, and neuroimaging work has found evidence for timing mechanisms in brain areas like the cerebellum (Grube et al., 2010a; Penhune et al., 1998; Teki et al., 2011), basal ganglia (Artieda et al., 1992; Grahn and Brett, 2007; Harrington et al., 1998; Teki et al., 2011), pre-SMA and SMA (Halsband et al., 1993; Kotz and Schwartze, 2011; Macar et al., 1999) and the premotor and prefrontal cortices (Buhusi and Meck, 2005; Coull et al., 2011). Motor areas are therefore believed to play a crucial role in temporal processing and this close

relationship between the motor system and timing has even led to statements such as 'limb movements are clocks' (Gooddy, 1958) and 'movement is time, expressed' (Teki et al., 2012).

Beat-based versus duration-based timing

Neuroimaging studies of rhythm perception and sensorimotor synchronization have shown consistent activity in subcortical structures like the cerebellum, basal ganglia, thalamus, and cortical structures such as the SMA, pre-SMA and premotor cortex (Bengtsson et al., 2009; Chen et al., 2006, 2008; Grahn and Brett, 2007; Grahn and Rowe, 2009), with the precise role of each of these areas still to be determined. However, studies have shown differential effects of deficits in the cerebellar and dopaminergic systems, and the suggestion has been made that there are two timing systems: absolute, duration-based timing and relative, beat-based timing (Teki et al., 2012). In this subdivision, the duration-based timing refers to the measurement of the absolute duration of discrete time intervals, while beat-based timing refers to the measurement of the duration of time intervals relative to a temporal regularity such as a beat.

On the one hand, studies have shown that the cerebellum is more active during non-rhythmic than rhythmic tasks (Grahn and Rowe, 2009; Teki et al., 2011), that cerebellar activity increases during tasks in which the beat becomes harder to detect (Kung et al., 2013), and that the cerebellum is more active during learning of non-metric than metric rhythms (Ramnani and Passingham, 2001). Moreover, cerebellar dysfunction disrupts performance during tasks that require absolute timing, with no effect on tasks requiring relative or beat-based timing (Grube et al., 2010a, 2010b). Cerebellar lesions have been shown to lead to selective impairments in the production of discontinuous movements but not in continuous rhythmic movements (Spencer et al., 2003). Therefore, although the cerebellum is consistently activated during beat perception and synchronization tasks, evidence indicates that the cerebellum is involved in absolute timing and not relative timing.

On the other hand, studies have shown that the nigrostriatal dopaminergic system and basal ganglia cortical projections to pre-SMA/SMA and the lateral premotor cortex play an important role in especially beat-based timing (Grahn, 2009; Grahn and Rowe, 2009; Kotz et al., 2016). Additionally, tasks with a strong rhythmic structure elicit more activity in the basal ganglia, pre-SMA/SMA and lateral premotor cortex than non-rhythmic tasks (Grahn and Brett, 2007; Grahn and Rowe, 2013; Teki et al., 2011), with the activity in the putamen and lateral premotor cortex being related to an internal beat prediction mechanism (Grahn and Rowe, 2013). This effect is not due to the fact that non-rhythmic tasks are more difficult than rhythmic tasks, as the increased activity is still seen when task difficulty is balanced (Grahn and Brett, 2007). The strongest evidence for the important role of the basal ganglia in relative timing comes from studies in PD patients. These have shown that deficient basal ganglia function specifically affects relative, beat-based timing and not absolute timing (Grahn and Brett, 2009).

Despite the fact that aforementioned studies suggest that there are two different timing systems that seem to use two different anatomical pathways (Teki et al., 2011),

it is important to mention that the beat-based and duration-based timing systems do, most likely, not operate independently, but in a coordinated fashion (Cope et al., 2014; Teki et al., 2012). For example, during entrainment, the beat-based system codes interval timing, and the duration-based network is simultaneously activated to carry out error correction (Teki et al., 2012).

Rhythm perception

The perception of a beat structure is a process that unfolds over time. First, the beat has to be found and after beat-finding, an internal representation of the beat can be made and used to predict future beats as the rhythm goes on. Recent work has shown that the basal ganglia, and specifically the putamen, are more involved in beat prediction than beat finding (Grahn and Rowe, 2013; but see Kung et al., 2013). This aligns with work showing that Area X in songbirds, the equivalent of the human basal ganglia (Brainard and Doupe, 2014), has an important role in melody generation (Miller et al., 2015). The finding that the basal ganglia (putamen) have an important role in rhythm generation or beat prediction (Grahn and Rowe, 2013), is particularly relevant for this thesis. Namely, as mentioned before, one important aspect of entrainment is the ability to produce rhythmic signals. Given the fact that PD patients suffer from deficient function of the basal ganglia, and these structures are important for internal rhythm generation and beat prediction, one would expect that PD patients are specifically impaired in tasks that require internal rhythm generation. This can, for example, be tested using synchronization-continuation tasks (SCT). In these tasks, an external rhythm is presented and subjects have to tap along with the rhythm (synchronization phase). After some time, the external stimulation is stopped and subjects have to continue tapping in the same pace (continuation phase). The synchronization phase tests the capacity to perceive the rhythm and to entrain to it, whereas the continuation phase tests the capacity to internally generate the rhythm and continue to tap at the same pace. These SCT-studies have indeed shown that PD patients have no problem during the synchronization phase, but are specifically impaired during the continuation phase (Elsinger et al., 2003; Tolleson et al., 2015; but see Pope et al., 2006). Moreover, results from studies using SCT-tasks show stronger putamen and SMA activation during the continuation than synchronization phase (Lewis et al., 2004), and results from patients with SMA lesions show a specific deficit in the continuation phase but not the synchronization phase (Halsband et al., 1993).

The optimal range for perception of music tempos is 1-3 Hz (Large, 2008), which is the frequency range of delta oscillations. Indeed, delta oscillations have been shown to phase align with the tempo of incoming stimuli for musical rhythms (Nozaradan et al., 2011, 2012), as well as for stimuli with less regular rhythms such as speech (Giraud et al., 2007). This alignment of neural oscillations with an external stimulus has led some to suggest that rhythm perception arises when non-linear oscillations in the nervous system entrain to external rhythmic stimuli, as proposed in neural resonance theory (Large and Snyder, 2009). This theory is in line with the idea of Darwin (see Section 1.2 of this Introduction; Darwin, 1871), because non-linear oscillations and their entrainment is intrinsic to the physics of the neural systems

involved (Large and Snyder, 2009). However, the simple alignment of oscillatory activity in auditory areas with an external rhythm is most likely not sufficient to explain beat perception. Namely, beat perception is not simply the discovery of periodicity in the input, but is more active and under voluntary control, as listeners can consciously alter a beat imposed on a rhythm (Nozaradan et al., 2011, 2012), and rhesus monkeys do not seem to perceive a beat when listening to auditory rhythms (Honing et al., 2012). Findings such as the engagement of motor areas by beat perception and musical training being associated with greater connectivity between motor and auditory cortices (Chen et al., 2008; Grahn and Rowe, 2009; Kung et al., 2013), suggest that beat perception is strongly linked to the motor system. Actually, several researchers have recently suggested that temporal prediction is accomplished in the motor system, perhaps through some sort of movement simulation (Arnal, 2012; Arnal et al., 2015; Schubotz, 2007), and that this information feeds back to sensory areas (through corollary discharges or efference copies) to enhance processing of incoming information at particular points in time. This bidirectional connectivity between auditory and motor regions is the basis for the Action Simulation for Auditory Prediction (ASAP) theory, which suggests that neural signals go from auditory to motor planning regions (among which premotor cortex, SMA and the basal ganglia) to provide information about the timing of auditory events, thereby influencing the timing of periodic motor planning signals in motor regions, and that these planning signals go from motor to auditory regions to provide a signal that predicts the timing of upcoming beats (Patel and Iversen, 2014). In particular, these temporal predictions appear to align the phase of delta oscillations in sensory cortical areas, such that stimuli that happen to be presented at phases of high excitability are processed more quickly (Lakatos et al., 2008), and more accurately (Arnal et al., 2015; Escoffier et al., 2010; Geiser et al., 2012) than stimuli presented at other times. As mentioned before, the phase alignment of the delta rhythm appears to be a neural instantiation of the Dynamic Attending Theory (DAT) (Large and Jones, 1999), whereby attention is drawn to particular points in time, and stimulus processing at those points is enhanced.

Interestingly, studies investigating neural oscillatory activity during SCT-tasks have shown specific roles for different frequency-bands. It was found in monkeys that gamma oscillatory activity is tuned towards the synchronization phase and that beta oscillations are particularly important during the continuation phase (Bartolo et al., 2014). This finding is in line with earlier work, associating gamma oscillations with sensory cued bottom-up signals (Fries, 2009; Kopell et al., 2000) and beta oscillations with top-down predictive signals (Arnal, 2012; Engel and Fries, 2010), forming the basis of the 'predictive timing' framework (Arnal and Giraud, 2012). The fact that (i) the basal ganglia and beta oscillations are both important for internal rhythm generation, (ii) the basal ganglia and beta oscillations both show abnormalities in PD, and (iii) that PD patients are specifically impaired in internal rhythm generation, makes it tempting to relate these to each other. However, whether these three findings are causally related to each other remains to be established. Nevertheless, it makes beta oscillations all the more relevant to the investigation into the neurophysiology of cueing in PD.

1.5 Outline of this thesis

The following chapters in this thesis are aimed at clarifying the neurophysiology of rhythmic cueing in Parkinson's disease, and the role of oscillatory entrainment in (temporal) prediction and attention. The research is presented in four chapters that will be introduced in more detail below.

First, in **chapter 2** I will investigate whether PD patients, like controls, can extract the temporal (and effector) predictability and use this information to entrain to the task rhythm and thereby improve motor performance. In this experiment, visual arrow stimuli instruct subjects to depress a button with either their left or right hand, depending on the direction of the arrow. The stimuli are presented in a rhythmic fashion, with the direction of the arrows being either random (allowing only entrainment to the temporal characteristics of the task) or predictable (allowing not only temporal, but also effector entrainment).

Since both conditions from the task in chapter 2 are presented using a fixed interstimulus interval, this study does not address the specific benefit of rhythmic over non-rhythmic stimulus presentation. Therefore, in **chapter 3**, I will focus on the question what the benefit of rhythmic stimulus presentation is, whether patients can extract the temporal regularities as well as control subjects do, and whether the neurophysiology underlying any positive effects of rhythmic versus non-rhythmic stimulation is similar for controls and patients. As in chapter 2, I will use a task with visual arrow stimuli requiring subjects to depress a button depending on the direction of the arrow. However, throughout this experiment the direction of the arrow stimuli is random (unpredictable), and I only manipulate the temporal characteristics of the stimuli. Specifically, in one condition the stimuli are temporally predictable by means of an isochronous stimulus presentation regime (allowing for entrainment), and in the second condition the stimuli are temporally unpredictable by varying the interstimulus intervals (allowing no or only suboptimal entrainment).

In **chapter 4**, I will investigate whether the reduced entrainment in PD, as found in chapters 2 and 3, is confined to the motor system or represents a more general deficit in entrainment. I aim to find an answer to this question by using rhythmic auditory stimulation and studying motor entrainment in both PD patients and healthy subjects using a target-detection task. At random time points, target stimuli will be omitted to investigate entrainment free from any stimulus-evoked activity or movement. Besides investigating the spontaneous entrainment to the stimulus rhythm, I will investigate more discrete motor preparation by varying target-likelihood on a trial-to-trial basis, instructed by the pitch of standard tones.

In the three experiments of chapters 2 to 4, stimuli are presented in the form of one single stimulus stream. This means that the cost of attending the task in a continuous instead of the more advantageous rhythmic mode, is relatively low. Now, entrainment is particularly advantageous in situations where multiple stimulus streams are presented and only one rhythmic stream has to be attended. Therefore, in **chapter 5**, I will study whether increasing the benefit of entrainment, by means of adding a distractor stimulus stream, elicits entrainment in PD patients equal to that shown by control subjects. This will answer the question whether motor entrainment in PD is impaired in general, or can be elicited but only under certain conditions that strongly encourage entrainment. I will use a target-detection task and present subjects an auditory or visual stimulus stream, either in isolation (unimodal

conditions) or while a stimulus stream of the other modality is presented in anti-phase (bimodal conditions), and subjects only attend the relevant stream.

Finally, in **chapter 6** I will discuss the empirical results of chapters 2 - 5 in the context of the role of behavioral and oscillatory entrainment in (temporal) attention and prediction, how these results contribute to our understanding of the neurophysiology of rhythmic cueing, and the implications of these findings for the role of oscillations in entrainment.

A shift from prospective to reactive modulation of beta-band oscillations in Parkinson's disease

Adapted from

A shift from prospective to reactive modulation of beta-band oscillations in Parkinson's disease.

te Woerd E.S., Oostenveld R., de Lange F.P., Praamstra P. (2014)

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2

Abstract

Increased beta (13–30 Hz) oscillatory synchrony in basal ganglia–cortical circuits is a physiological characteristic of Parkinson's disease (PD). While the function of the beta rhythm is unknown, there is evidence that its modulation serves a predictive role, in preparation of future actions. We investigate the relation between predictive beta modulation and entrainment of brain oscillations in a task inviting behavioural entrainment by a regular task structure. MEG was recorded during a serial choice response task, in a group of 12 PD patients and 12 control subjects. In one condition, the reaction stimuli allowed for temporal preparation only (random condition), while in a second condition (predictable condition) the reaction stimuli allowed both temporal and effector preparation. Reaction times were identical between groups, and both groups benefited equally from the known effector side in the predictable condition. Analysis of oscillatory activity, by contrast, revealed marked differences between groups. In patients, the proportion of preparatory beta power desynchronization preceding the reaction stimuli was significantly smaller than in controls, while the proportion of beta desynchronization following the events was larger. In addition to this shift from prospective to reactive modulation of beta-band oscillations, patients showed a trend to reduced motor cortical pre-stimulus delta phase synchronization, and later gamma power synchronization than controls. Delta phase synchronization was, furthermore, significantly correlated with predictive beta desynchronization, supporting the relevance of hierarchical coupling between oscillations of different frequencies for the analysis of oscillatory changes in PD. Together, these features of task-related oscillatory activity indicate that entrainment fails to engender the same predictive mode of motor activation in PD patients as in healthy controls.

2.1 Introduction

It is well-established that basal ganglia dysfunction in Parkinson's disease (PD) is accompanied by an excess of oscillatory synchrony in the beta band (for reviews see Boraud et al., 2005; Hammond et al., 2007). This holds true for local field potentials in the basal ganglia and, less frequently observed, cortical beta oscillations measured by means of EEG or MEG (Crowell et al., 2012; Pollok et al., 2012). Correlations between clinical improvement and attenuation of STN beta power by dopaminergic medication and/or deep brain stimulation of the STN (Giannicola et al., 2010; Kühn et al., 2008; Ray et al., 2008) have suggested that high beta power may contribute to parkinsonian bradykinesia and rigidity. The possibility of a causal rather than epiphenomenal relation is supported by evidence that driving of cortical activity at beta frequencies slows down movement (Joundi et al., 2012; Pogosyan et al., 2009).

Within the context of research on the basal ganglia and PD, there is recent emphasis on beta modulation having an anticipatory role (Jenkinson and Brown, 2011; Oswal et al., 2012). Beta power is both down-regulated following a cue to prepare a movement, and up regulated in anticipation of a postural challenge (Androulidakis et al., 2007a). Such features of beta activity underlie the proposal that beta activity in the basal ganglia and cortex may form an "internal likelihood index of the need for a novel voluntary action" (Jenkinson and Brown, 2011), driven by salient internal and external cues. The prospective nature of beta power modulation is a feature that beta oscillations share with slow brain potentials such as the readiness potential (RP) and the contingent negative variation (CNV). Indeed, both RP and CNV are sensitive to altered (movement) preparatory processes in PD (Cunnington et al., 1995; Jahanshahi et al., 1995; Praamstra et al., 1996a, 1996b; Praamstra and Pope, 2007; Wascher et al., 1997).

The observation that compromised preparatory processes in PD are reflected in slow brain potentials as well as beta oscillations may be more than coincidental, especially if slow brain potentials are due to phase resetting of slow oscillations (Schroeder and Lakatos, 2009; Stefanics et al., 2010). A rapidly accumulating body of work has outlined a hierarchical coupling between oscillations of different frequencies (Canolty et al., 2006; Cravo et al., 2011; Lakatos et al., 2005, 2008). Slow oscillations in the delta frequency range have been shown to synchronize to environmental events that occur in a regular pattern. Faster oscillations, in turn, synchronize their phase and/or amplitude to the slow oscillations. Since alternating phases of neural oscillations correspond to low and high membrane excitability, the synchronization and hierarchical coupling could serve the purpose of bringing the relevant brain structures from which the oscillations originate into an optimal state for processing the stimuli to which they synchronize (Lakatos et al., 2005). Importantly, in any environment with events occurring at regular intervals, oscillatory synchronization may establish itself automatically, as it enables a more efficient rhythmic/predictive mode of attending compared to the continuous vigilant mode necessitated by an unpredictable environment (Cravo et al., 2013; Schroeder and Lakatos, 2009).

Against this background, the behaviour of beta activity in cognitive or motor tasks with a regular task structure provides a means for addressing the following issues. Firstly, whether the presumed predictive nature of beta power modulation

(Jenkinson and Brown, 2011) also applies when prediction is not driven by explicit knowledge, but the result of entrainment. Secondly, whether predictive modulation of beta power is linked to entrainment of slower and faster oscillations. In a previous EEG study, we already found evidence for altered entrainment in PD (Praamstra and Pope, 2007). However, this work described altered beta modulation in a qualitative fashion only, while analysis of slow brain activity was limited to time domain analysis using the CNV. Here, we employed MEG to readdress altered entrainment of oscillatory activity in PD patients, using a choice response task with a fairly fast rate of stimulus presentation to induce entrainment.

The aims of the study were, firstly, to confirm that PD specifically compromises predictive modulation of beta activity, i.e., attenuation of beta power preceding the reaction stimuli. Secondly, to examine hierarchical coupling of oscillatory activity, we evaluated whether altered beta modulation is associated with reduced synchronization of slow oscillations in the delta frequency range. Thirdly, we searched for signs of altered entrainment of gamma synchronization. Gamma activity is involved in movement production and is increased by dopaminergic medication (Alegre et al., 2005; Androulidakis et al., 2007b; Devos et al., 2006). Altered entrainment of gamma along with deficient entrainment of beta activity provides additional support for hierarchical coupling of oscillations. Finally, to gain a better perspective on the relation between oscillatory changes and anticipatory behaviour, we contrasted a condition allowing only temporal preparation with a condition promoting both temporal and effector preparation. The latter condition enhanced the salience, in an implicit fashion, of the predictable task structure, perhaps eliciting entrainment in PD patients when it is not shown with just temporal predictability of response signals.

Although this study examines entrainment of MEG-recorded brain oscillations in conjunction with temporal and motoric entrainment of upper limb movements, our study also aims to contribute to the neurophysiology of (gait) cueing in PD. Translated to this domain, the results indicate that, in PD, rhythmic stimulation does not engender the same predictive motor activation as it does in healthy subjects.

2.2 Materials and methods

Participants

Participants were 12 PD patients (nine men; mean age ± SD, 57 ± 5 years) and 12 healthy control subjects (seven men; age 57 ± 5 years). The control subjects were without history of neurological or psychiatric disease. The PD patients were of mild to moderate disease severity. In the PD group there were two left-handers and in the control group one, as determined by self-report. Left-handers were not excluded because the task involved both hands and MEG analyses were conducted in terms of contra- and ipsilateral hemispheres. All participants had normal or corrected-to-normal vision. Participation was based on informed consent according to the Declaration of Helsinki and the study was approved by the local ethics committee (CMO Arnhem-Nijmegen). All patients were on dopaminergic medication and had a mean score of 26 (±6) on the motor section of the Unified Parkinson's Disease

Rating Scale (UPDRS) (see Table 2.1). Disease duration ranged between 1 and 12 years (mean 6 years), with the most affected side being the right (n=7) and left (n= 5). While all patients' motor symptoms were asymmetric, both sides were affected in all and asymmetry was modest. The reported analyses of behavioural and neurophysiological data do not differentiate between most and least affected sides, as there were no significant differences. The investigation and UPDRS rating were always performed in the morning, after overnight withdrawal of medication (>12 h).

Table 2.1 Demographics and clinical characteristics of participating Parkinson patients. Levodopa was always used with dopadecarboxylase inhibitor carbidopa or benserazide.

Subject number	*Age (yrs) and gender*	*Years since diagnosis*	*Most affected side*	*UPDRS motor score*	*Dominant hand*	*Medication (daily dose)*
1	60, M	9	R	35	L	Levodopa 1400 mg
2	64, M	20	R	39	R	Levodopa 950 mg Entacapone 800 mg Pramipexol 0.875 mg
3	54, M	1	R	21	L	Levodopa 300 mg
4	52, F	5	R	24	R	Levodopa 450 mg
5	54, M	5	R	29	R	Levodopa 500 mg
6	59, M	11	R	22	R	Levodopa 450 mg Pramipexol 3.75 mg
7	61, M	10	R	21	R	Levodopa 550 mg
8	53, M	1	L	26	R	Levodopa 300 mg Artane 6 mg
9	67, F	12	L	29	R	Levodopa 500 mg Pramipexol 3.75 mg Amantadine 200 mg
10	62, F	2	L	16	R	Levodopa 450 mg Pramipexol 1 mg
11	55, M	5	L	24	R	Levodopa 500 mg Ropinirol 4 mg
12	52, M	1	L	24	R	Levodopa 450 mg

Task and procedure

The experiment consisted of a choice response task to arrow stimuli presented on a screen, with the choice response being a left or right index finger button press. The critical experimental manipulations concerned the timing and the order of successive stimuli or trials. The response signals were presented at a relatively fast rate and fixed SOA (stimulus onset asynchrony), except for the last stimulus. The fast rate and fixed SOA were designed to induce temporal entrainment. The deviant final SOA, following trial series of variable length, helped to assess whether entrainment occurred. The predictability of a left or right hand response was manipulated by using two types of experimental blocks, presented in alternating fashion. In one version (the "random" condition), the order of the left and rightward

pointing arrows was random. In the other version (the "predictable" condition), the response hand was predictable by alternating presentation of the left and rightward pointing arrows.

The experiment was divided in eight blocks of ~6 min each. Within each block, individual trials were presented in series of 11, 13, 15 or 17 consecutive trials and each block contained eight series. The variation in trial number served to prevent subjects from counting down to the end of the series. In each series, the SOA between successive reaction stimuli was always 1.5 s except for the last trial, which followed a SOA of 1.25 s or 1.75 s, that is 250 ms shorter (short deviant) or 250 ms longer (long deviant) than the preceding SOAs. Between each series there was a break of 19.875 s, 20.25 s, 20.625 s or 21 s. This was done in order to start the next series out of phase with the previous series. Between blocks there was a break of at least 1 min. The total number of series presented was 64, equally divided in random and predictable series. Responses to each stimulus were made with the left or right index finger, depending on the direction of the arrow.

The experiment was preceded by a short practice block that contained series from both conditions. Participants were not made aware of the regularity in SOA, the sequence-final deviant SOA, or the predictability of response hand in the predictable condition. The stimuli were presented with Presentation 14.9 software (Neurobehavioural Systems), using a liquid crystal display video projector, and back projected onto a translucent screen with two front-silvered mirrors. Participants were seated comfortably in the MEG-chair with their eyes 75 cm from the screen. Response keys were attached to the armrests of the chair and subjects rested their fingers on the keys. Arrow stimuli were presented in white on a gray background for 300 ms. A fixation area was indicated by permanently displayed white brackets surrounding the central screen area where the arrow stimuli were presented. The brackets enclosed a square of 7.2° × 6.1° of visual angle; the arrows measured 1.2° × 1.2° of visual angle.

MEG recordings

Ongoing brain activity was recorded using a whole-head MEG system with 275 axial gradiometers (VSM/CTF Systems, Coquitlam, BC) in a magnetically shielded room. During the experiment, we continuously measured head position relative to the sensor array using localization coils that were placed at the nasion and in the left and right ear canals. Furthermore, we recorded vertical electro-oculogram (EOG) from the supraorbital and infraorbital ridges of the left eye, and horizontal EOG from the bilateral canthi. MEG and EOG data were sampled at 1200 Hz.

Behavioural analyses

Reaction time analyses were performed on the responses following standard and deviant SOAs. For analysis of responses following standard SOAs, the first two trials of each series were discarded. In addition, we excluded trials with erroneous responses and outliers (±3 SD from the individual mean). Mean response times were determined for each condition separately. Differences in mean reaction times

for standards were assessed using a mixed-design repeated measures analysis of variance (ANOVA) in SPSS version 19 (IBM Corp. Armonk, NY) with the between-subjects factor Group (controls vs. PD patients) and the within-subjects factor Predictability (random vs. predictable). An additional analysis assessed differences between reaction times for standards and deviants with a 3-level within-subjects factor SOA (short vs. standard vs. long).

MEG data preprocessing

MEG data were analyzed with MATLAB 7 (Mathworks, Natick, MA) using the open-source FieldTrip toolbox (Oostenveld et al., 2011). For the main analysis, epochs of 5000 ms (2000 ms pre-stimulus and 3000 ms post-stimulus) were extracted from the continuous data separately for both task conditions and response sides. Epochs were checked for artifacts using a semiautomatic routine detecting and rejecting trials containing muscle artifacts, slow drift, or SQUID (superconducting quantum interference device) jumps. After removal of artifacts, data were down-sampled to 300 Hz. Then, independent component analysis (ICA) was used to remove any remaining variance caused by eye blinks and heartbeat artifacts. Two control subjects and one PD patient showed a slow drift artifact which was removed by additional principal component analysis. As an extra check, the remaining data epochs were visually inspected and any remaining epochs with artifacts were removed manually. The remaining stimulus-locked datasets were submitted to time-frequency and statistical analyses.

From the axial gradiometer data, a planar gradient transform was calculated (Bastiaansen and Knösche, 2000). The planar representation simplifies the interpretation of the sensor-level data because it concentrates the maximal activity above the source. Frequency decomposition was performed on the horizontal and vertical components of each channel, and these components were subsequently combined to obtain the oscillatory power at each synthetic planar channel. For all channels, time frequency representations (TFRs) were calculated using a Fourier transform approach, applied to short sliding time windows across the entire length of the epochs, with a step-size of 50 ms. Before the Fourier transform, one or more tapers were multiplied to each time window and the resulting power estimates were averaged across tapers. The mean planar gradient power was estimated for all trials within a condition. For the frequencies 1–30 Hz (1 Hz frequency resolution), a single Hanning taper and an adaptive time window of four cycles for each frequency were used. For the frequencies 30–130 Hz, a fixed taper length of 250 ms was used (4 Hz frequency resolution, but increased to 2 Hz by spectral interpolation) as well as a frequency smoothing of $\Delta f = 20$ Hz (Percival and Walden, 1993), resulting in four tapers. Percentage change in oscillatory power was defined as the relative change with respect to the mean of the epoch (1000 ms pre-stimulus to 2000ms post-stimulus). The epoch length included two trials, enabling better comparison between predictable and random conditions.

Sources of beta activity were identified using a frequency-domain beam-forming approach on the axial sensor data. We contrasted the beta event-related desynchronization (ERD) (0–0.5 s post-stimulus) with the beta event-related

synchronization (ERS) (0.6–1.1 s post-stimulus) activity for the beta frequency band (13–30 Hz). As the beam-former input required only one frequency, we used the center frequency of the beta band (22 Hz, resulting in 11 full cycles per time window). A realistic single-shell head model (Nolte, 2003) was created for all individuals using the brain surface from their individual segmented MRIs (11 out of 12 controls, 8 out of 12 PD patients) or a MNI template-MRI (Holmes et al., 1998). The brain volume of each individual was discretized to a grid with an 8 mm resolution and the lead field matrix was calculated for each grid point according to the head position in the system and the forward model. A spatial filter was then constructed for each grid point using the covariance and the lead field matrices. Source strengths were calculated for the ERD and ERS windows, after which these were contrasted and the location coordinates of maximal difference were saved for use in the analysis of delta phase.

MEG analyses

Beta activity

Since beta oscillatory activity (13–30 Hz) is most prominent in the sensorimotor system, and lateralizes with unimanual responses, sensorimotor region ROIs were determined by a subtraction of beta activity associated with the left and right hand responses. This subtraction was performed across conditions and groups. Subsequently, the 20 sensors with the strongest beta modulation above each hemisphere were selected. After rejecting any sensors without a homologous sensor over the opposite hemisphere, this left two symmetric ROIs overlying the sensorimotor cortices each consisting of 18 sensors (see Fig. 2.3). In addition to analyses of beta power in sensorimotor ROIs, beta power was also analyzed across all sensors, using cluster-based non-parametric permutation tests (Maris and Oostenveld, 2007) in FieldTrip.

To study beta modulation over time, power values were averaged over the entire beta band and all sensors per ROI, creating contra- and ipsilateral time series of beta power. Time series for the left and right hand response conditions were combined by averaging the conditions separately for the contra- and the ipsilateral hemisphere. Modulation depth of beta power was defined as the difference between maximum post-stimulus desynchronization and synchronization. Differences in beta modulation depth were statistically tested using a mixed-design repeated measures ANOVA with between-subjects factor Group and within-subjects factors Predictability and Hemisphere. The amount of predictive beta modulation was defined as the percentage of desynchronization that occurred before stimulus onset, relative to the total desynchronization depth (difference between maximum pre-stimulus synchronization and post-stimulus desynchronization), and were both analyzed with the same ANOVA.

Gamma activity

For analysis of changes in gamma band power (60–90 Hz), two ROIs were identified in a similar way as for beta activity. First, a subtraction of activity associated with the left and right hand responses was performed to reveal the spatial distribution in

a 350–550 ms post-stimulus time window. This subtraction was performed across conditions and groups. Since the distribution of gamma activity was captured reasonably well by the ROIs for beta power changes, these ROIs were optimized by removing three sensors at the ROIs medial border and adding three sensors at the lateral border, thus shifting the ROIs slightly laterally. This left two symmetric ROIs overlying the sensorimotor cortices each consisting of 18 sensors. After defining ROIs, the time course of gamma power was estimated by averaging spectral power across the frequency band and over all sensors of the ROI. Because of the relatively low signal-to-noise ratio of the gamma modulation, onset latencies of gamma ERS and peak gamma ERS were analyzed with a jackknifing procedure. In this procedure, every participant's gamma power trace over time was replaced by a subaverage across the other n – 1 participants of the group, separately for controls and patients (Ulrich and Miller, 2001). Onset of gamma ERS was determined as the time point of minimal gamma power in the interval 400 ms pre-stimulus to 200 ms post-stimulus. The subsample gamma ERS onset latencies were submitted to a mixed-design ANOVA with between-subjects factor Group and within-subjects factor Predictability. The gamma ERS peak latency was defined as the time point of maximal gamma power in the interval 200–600 ms post-stimulus and was analyzed in the same way. To correct for the reduced variance of subsample gamma onset latencies due to the jackknifing procedure, F-values were adjusted according to Ulrich and Miller (2001).

Delta activity

Delta phase analysis was performed on spatially filtered data using a time-domain beam-former spatial filter (linearly constrained minimum variance). This beam-forming spatial filter for the previously stored locations of interest (the sensorimotor cortex, estimated by the source of beta activity) was used to filter the MEG data, separately for contra and ipsilateral hemispheres. The LCMV spatial filter passed the activity at the location of interest with unit-gain, while optimally suppressing all other noise and other source contributions to the MEG data. Data epochs (from 2 s pre-stimulus to 3 s post-stimulus) were band-pass filtered between 0.05 and 3 Hz using a finite impulse response least squares filter. Instantaneous delta phase values were calculated using the Hilbert transform of the band-pass filtered data. To test if any phase preference was present for the instantaneous phases at stimulus onset, Rayleigh's test for uniformity of phase data was used (Fisher, 1993). The strength of phase preference (entrainment) was acquired by calculating the intertrial coherence (ITC) over all trials within each individual. The ITC ranges from 0 to 1, where 0 means no phase consistency and 1 is perfect phase consistency. Rayleigh's test and ITC calculations were performed using the MATLAB circular statistics toolbox (Berens, 2009). All ITC values were submitted to a mixed-design ANOVA using between-subjects factor Group and within-subjects factors Predictability and Hemisphere. Pearson correlations were calculated in SPSS version 19 (IBM Corp. Armonk, NY) to test for any correlations between the amount of predictive beta modulation and the delta ITC.

2.3 Results

Behavioural data

Participants had to press a button with their left or right index finger after presentation of a left or right pointing arrow. The mean response times were approximately 100 ms faster in the predictable condition (controls: 331 ± 76 ms, PD patients: 353 ± 80 ms) compared to the random condition (controls: 437 ± 80 ms, PD patients: 454 ± 80 ms), yielding a significant main effect of Predictability ($F(1,22) = 241.5$, $P < 0.0001$) (see Fig. 2.1A). There was no significant difference between controls and patients across conditions ($F(1,22) < 1$), nor was there an interaction between Group and Predictability ($F(1,22) < 1$), indicating that both groups benefitted equally from effector predictability. Error rates were not different between groups in the random (controls: 3.5%, PD patients: 3.3% ($F(1,22) < 1$)) nor in the predictable condition (controls: 7.2%, PD patients: 2.7% ($F(1,22) = 2.5$, $P = 0.13$)).

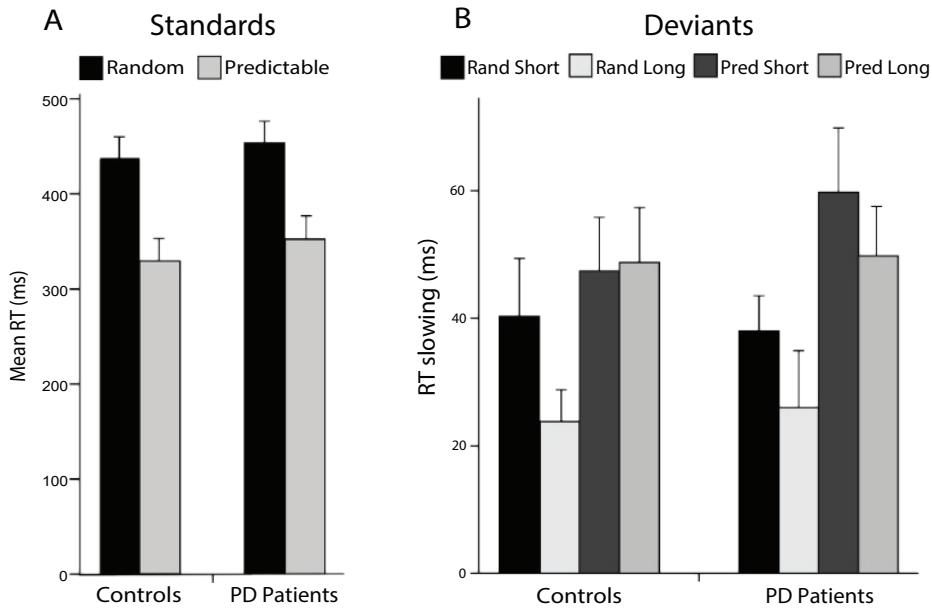

Figure 2.1 (A) Mean group reaction times following stimuli at the standard SOA in the random and predictable conditions. Values are in ms and error bars represent 1 standard-error-of-the-mean (SEM). Reaction times are averaged over the left and right hand responses. (B) Mean slowing in reaction time (relative to reaction time following standard SOA) for responses following short and long deviants SOAs.

The deviant final SOAs led to violations of temporal expectation, inducing longer reaction times. An omnibus analysis across standards and deviants showed this effect to be significant ($F(1.9,41.7) = 47.9$, $P < 0.0001$) (see Fig. 2.1B). The reaction times to deviants were further analyzed separately, and reported in terms of the RT-increment relative to standards. There were no significant main effects or interactions involving the factor Group. There was, however, a significant main effect of Predictability ($F(1,22) = 134.1$, $P < 0.0001$). This was due to the mean response time increment following deviant SOAs being significantly larger in the predictable than in the random condition. Thus, violations of temporal expectancy

are more disruptive when not only the upcoming stimulus is temporally predictable, but also the effector is already prepared. There was a tendency for the cost of timing perturbations to be modulated by their direction, as reflected in a marginally significant effect of the direction of SOA deviance ($F(1,22) = 3.1$, $P = 0.09$). The difference between conditions was in the expected direction. As described by Grosjean et al. (2001), when an anticipated stimulus occurs earlier than expected, then its backward shift in time will be partly reflected in a longer RT, whereas a later presentation tends to shorten the RT.

Oscillatory brain activity

Distribution of sensorimotor beta activity

Time–frequency analyses showed predominant movement-related modulations in the beta band. We first evaluated the distribution of the beta modulation, by quantifying beta power peak-to-peak from maximum desynchronization to maximum synchronization (see Fig. 2.3). The modulation of beta activity was maximal over the sensorimotor cortex contralateral to the response hand, and appeared to be more lateralized in the predictable than in the random condition (see Fig. 2.2). As shown in the time–frequency plots of Fig. 2.3, the modulation of beta power occurred over the full beta range from 13 to 30 Hz. The beta modulation followed a fixed pattern, with a reduction in beta power (desynchronization) before and during movement, and a subsequent increase in beta power (synchronization) shortly after movement.

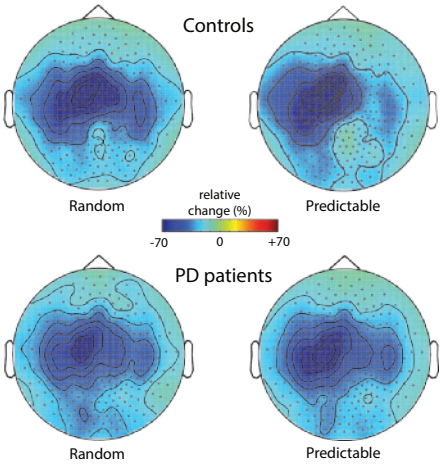

Figure 2.2 Distribution of the mean beta power modulation (% change), as measured from maximal ERD to maximal ERS. Topographies are averaged over the left and right hand responses by first mirroring the topographies of the left hand condition over the anterior–posterior axis and then averaging over the right and left hand conditions. Thus, the left hemisphere sensors are contralateral, and the right hemisphere sensors ipsilateral to the side of movement.

Effects of effector predictability

A prominent feature in the time-frequency plots (Fig. 2.3) is an apparently earlier (contralateral) beta desynchronization in the predictable compared to the random condition. This was statistically evaluated by means of a cluster randomization analysis over all sensors. Beta power (13–30 Hz) was compared between predictable and random conditions in a 200 ms pre-stimulus time window. The analysis confirmed that pre-stimulus beta power showed a stronger attenuation in the predictable than in the random condition in clusters overlying the sensorimotor cortex contralateral to the upcoming response hand (see Fig. 2.4). This was the case in controls for both left ($P < 0.001$) and right hand ($P < 0.001$) responses. This was likewise the case in PD patients for the left ($P < 0.04$) as well as right hand ($P < 0.003$) responses. This

analysis demonstrates that the marked reaction time advantage in the predictable condition is indeed achieved, in both groups, on the basis of effector preparation as indexed by lateralized beta-band suppression.

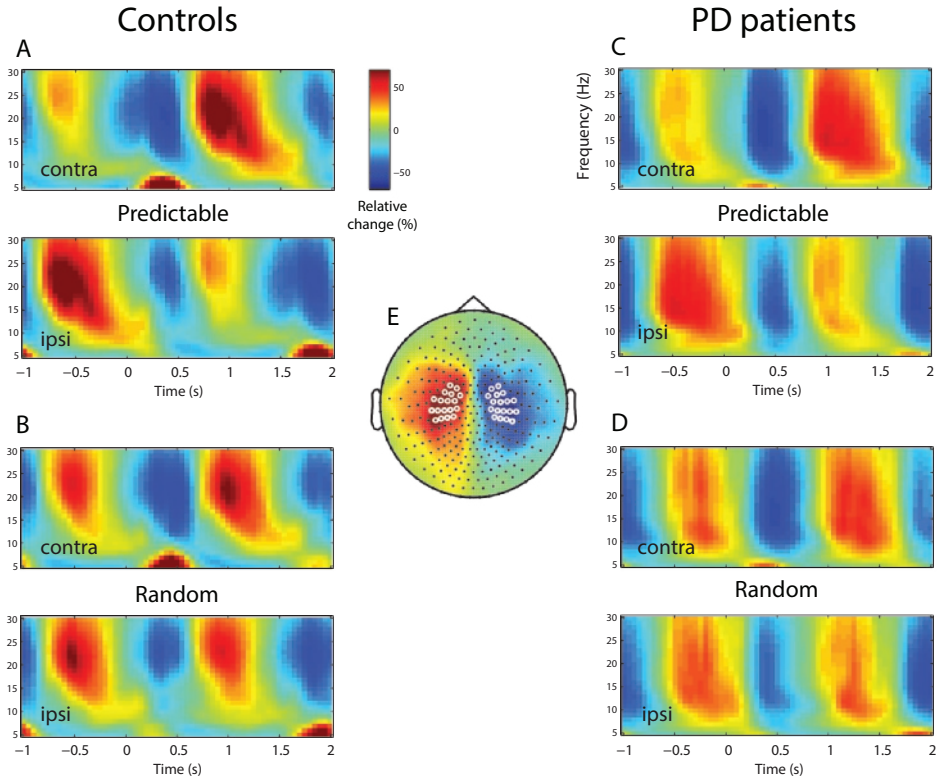

Figure 2.3 Group mean time–frequency representations of oscillatory power changes, relative to the mean power over the epoch. Data of control subjects are on the left (predictable (A) and random (B) conditions). Data of PD patients are in the right column (predictable (C) and random (D) conditions). Time–frequency data are mean spectral power values over ROIs represented in (E). T = 0 indicates onset of the stimulus requiring a contralateral hand response.

Temporal dynamics of beta modulation

The time course of beta modulation shows a repeating pattern of beta desynchronization and synchronization. Since this oscillating pattern does not allow the definition of a pre-stimulus baseline, Fig. 2.5 shows the time series aligned to a baseline defined relative to the time of stimulus presentation. The modulation of beta power over time was analyzed in terms of two properties, the modulation depth as an indicator of the dynamic range of beta power changes and the amount of predictive modulation as an indicator of preparatory activity for an upcoming stimulus or response. These indices of beta modulation were deemed more appropriate for the analysis of beta activity during the relatively fast movement sequences, and yield more information on the temporal dynamics of the beta modulation, than an analysis in terms of beta-ERS and ERD relative to beta power in a resting period.

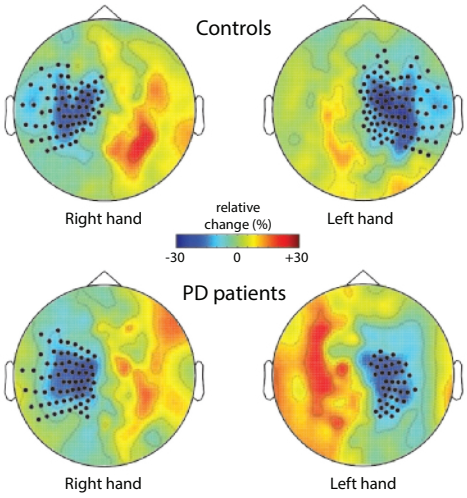

Figure 2.4 Significant differences in group mean beta power changes between predictable and random conditions, measured in a 200 ms pre-stimulus window. Significant clusters of sensors in overlying areas with stronger beta ERD in the predictable compared to the random condition are marked with black dots. The color scale represents the difference in relative change (%) of beta power between conditions.

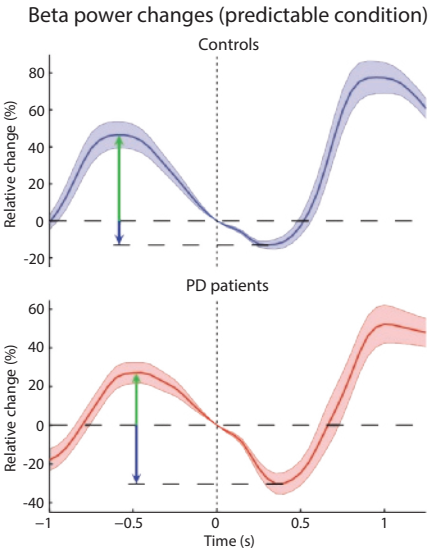

Figure 2.5 Time course of group mean beta power changes over the contralateral sensorimotor cortex ROI in the predictable condition. The traces represent power values over the entire beta band (13–30 Hz); the shaded margin represents ± 1 SEM. The predictive beta modulation was calculated as the percentage of beta ERD that occurred before stimulus onset, i.e. the change in power from pre-stimulus beta-ERS peak to t= 0 (indicated by the vertical green line) relative to the full ERD depth and the change from pre-stimulus beta-ERS peak to post-stimulus beta-ERD trough (indicated by the vertical green plus dark blue line). Note that this calculation is independent of the baseline definition. To facilitate visual comparison of the pre- and post-stimulus changes in beta power between groups, the power traces are baselined at time point zero.

The modulation depth was significantly larger in the hemisphere contralateral than ipsilateral to the response hand, for all conditions and groups ($F(1,22) = 62.7$, $P < 0.0001$). There was also a significant interaction between Predictability and Hemisphere ($F(1,22) = 15.1$, $P < 0.001$), as the contralateral modulation depth was larger in the predictable than in the random condition. The ipsilateral modulation depth showed the opposite effect, being smaller in the predictable than in the random condition. No differences were found in modulation depth between groups ($F(1,22) < 1$).

Predictive beta modulation was calculated as the percentage of beta modulation that occurred before stimulus onset compared to the total depth of the beta ERD (see Fig. 2.5). Analysis results for predictive beta modulation are summarized in Fig. 2.6. Across groups, there was significantly more predictive beta modulation in the hemisphere contralateral to the response hand than in the ipsilateral hemisphere ($F(1,22) = 27.7$, $P < 0.0001$) and there was an interaction between Hemisphere and Predictability ($F(1,22) = 24.4$, $P < 0.0001$). The interaction was explained by the fact that the difference in predictive beta modulation between hemispheres was

larger in the predictable than in the random condition. Importantly, there was also a significantly lower predictive beta modulation in PD patients compared to controls across conditions ($F(1,22) = 8.8$, $P < 0.007$). No interactions were found involving the factor Group. Since there was no difference in the depth of the full ERD between groups ($F(1,22) < 1$), the lack of predictive beta modulation in patients is made up for by a stronger reactive modulation, a feature which is evident in Fig. 2.5. By virtue of the definition of predictive beta modulation relative to the full ERD, the group difference in reactive beta modulation is identical to the difference in predictive beta modulation.

The altered contribution of predictive and reactive modulation to the total amount of task-related beta modulation was confirmed by an analysis of the instantaneous phase of contralateral beta power changes at stimulus onset. There was a significant difference between Predictability conditions ($F(1,22) = 54.5$, $P < 0.0001$), explained by beta power being further advanced towards the ERD trough of the modulation cycle, at stimulus onset, in the predictable compared to the random condition. The instantaneous phase of the beta power modulation at stimulus onset was also different between groups ($F(1,22) = 5.5$, $P < 0.03$), where beta power of controls was closer to the beta trough (maximal ERD) than for PD patients (see Fig. 2.7).

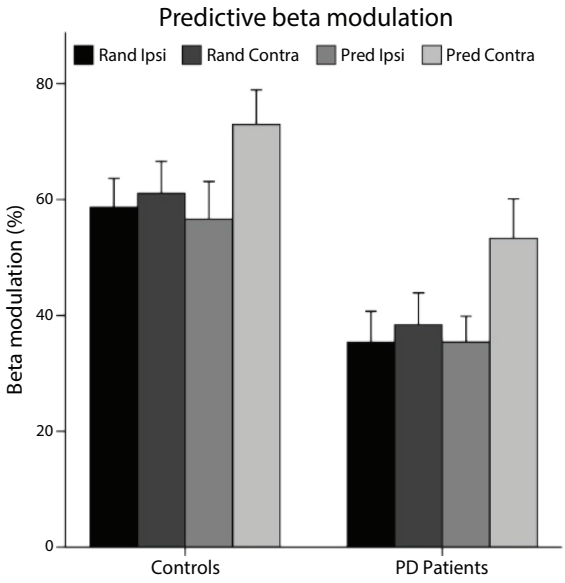

Figure 2.6 Predictive beta modulation, i.e. the percentage of the beta ERD that occurs before stimulus onset, relative to the full depth of the ERD. The group mean percentage of predictive beta modulation (error bars represent 1 SEM) is shown for both groups in the random and predictable conditions, and ipsi- and contralateral hemispheres.

This phase difference in the cycle of beta power changes indicates that in control subjects more ERD is completed before stimulus onset than in PD patients. There were no interactions involving the factor Group. This additional analysis underscores that the difference in predictive beta modulation between patients and controls is not the result of our choice of baseline.

In order to verify the behavioural relevance of predictive beta modulation, we computed the correlation between predictive beta modulation and reaction time. The Pearson correlation (across groups), between predictive beta modulation in the hemisphere contralateral to the upcoming response hand and reaction time was significant in both the random ($r = -0.54$, $P < 0.01$) and the predictable ($r = -0.46$, $P < 0.03$) condition (see Fig. S2.1).

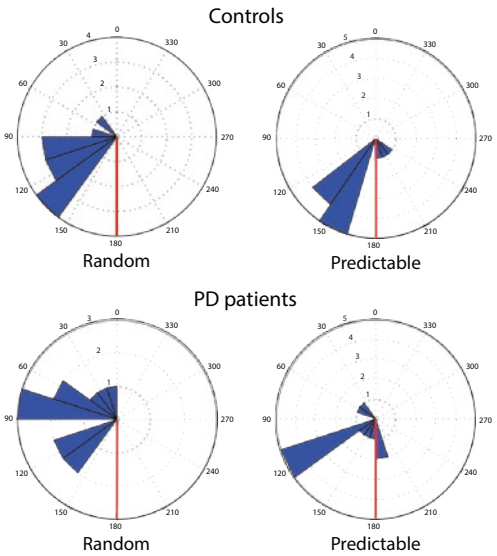

Figure 2.7 Instantaneous phase (in degrees) of contralateral beta power changes at stimulus onset for both groups (control subjects and PD patients) and conditions (predictable and random). The red line indicates the beta trough (maximal ERD).

Spectral power in rest

Although it is unlikely that the task-related modulations of spectral power are influenced by differences in resting power between groups, we analyzed spectral power for all participants during rest, i.e. in-between the trial series. Spectral power was analyzed over the same ROIs as used in the analysis of task-related beta power. There was no difference in spectral power in rest between blocks of predictable or random arrow stimuli ($P > 0.50$, using a permutation test over all frequencies with 1000 randomizations). Hence the resting periods before predictable and random trial series were combined per participant. Spectral power during rest was compared between groups using a permutation test over all frequencies (1000 randomizations), and showed that there was only a significant difference in power in the theta band. That is, PD patients had higher power between 6.3 and 7.5 Hz ($P < 0.05$). Additionally, mean spectral power over the alpha (8–12 Hz) and beta (13–30 Hz) bands was tested separately by using a one-way ANOVA with between-subjects factor Group. There was no difference between groups in mean spectral power over the alpha ($F(1,22) = 2.0$, $P > 0.16$) or beta ($F(1,22) = 1.7$, $P > 0.20$) bands.

Temporal dynamics of gamma modulation

Given the more reactive nature of beta modulation in PD patients, we subsequently asked if the modulation of gamma power also had a more reactive profile. Gamma activity was studied over two clusters of 18 sensors symmetrically distributed over both hemispheres (see Materials and methods). Time–frequency representations of gamma power changes over the hemisphere contralateral to the response hand are shown in Fig. 2.8. Evaluation of the time–frequency spectra suggested that movement-related gamma activity in control subjects increased earlier than in PD patients, as can be seen in Figs. 2.8A and B.

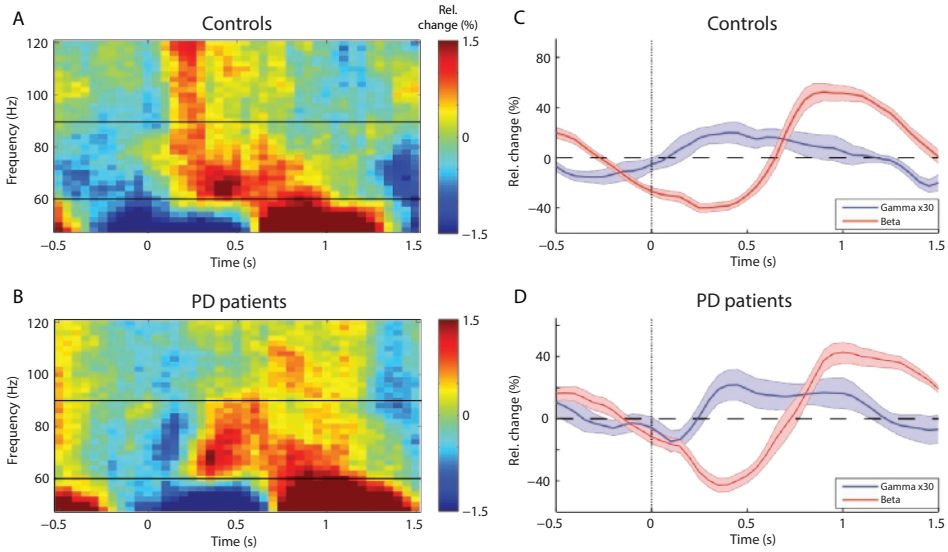

Figure 2.8 Time–frequency representations of gamma activity over the contralateral sensorimotor ROI in the predictable condition. (A) Controls. (B) Patients. The analyzed gamma band (60–90 Hz) is indicated by horizontal black lines. (C) and (D) show the time courses of mean contralateral power changes, in the predictable condition, for the beta (13–30 Hz) band in red, and the gamma band (60–90 Hz), in blue (the traces are represented ± 1 SEM, indicated by the shaded areas). The traces are aligned relative to the mean across the epoch.

The time courses of beta and gamma power changes showed, as expected, an inverse relationship between beta and gamma power changes. Importantly, where the anticipatory decrease in beta power in controls was accompanied by an early slow increase in gamma power (Fig. 2.8C), the more reactive beta ERD in PD patients was accompanied by a similar reactive gamma ERS (Fig. 2.8D). The onset of gamma-ERS was evaluated with a repeated measures ANOVA, which confirmed a significant difference between groups in the form of an interaction between Predictability and Group ($F(1,22) = 5.8$, $P < 0.025$). The main effect of Group did not reach significance ($F(1,22) = 3.4$, $P = 0.1$). Post-hoc testing showed that in the predictable condition, the onset of gamma ERS was significantly later in patients than in controls ($F(1,22) = 6.3$, $P < 0.025$), while there was no difference in onset of gamma ERS in the random condition ($F(1,22) < 1$). In contrast to the onset latency of the ERS rise, the time point of maximal gamma ERS did not differ between conditions ($F(1,22) < 1$) and groups ($F(1,22) < 1$). Nor was there a significant interaction.

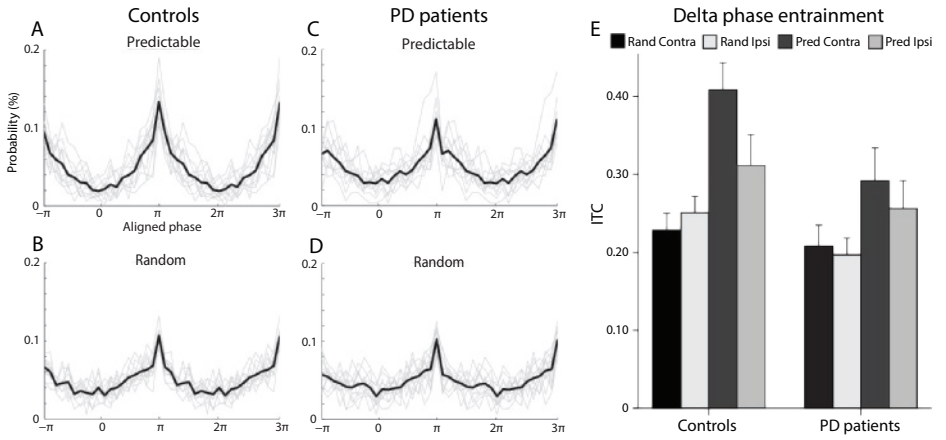

Figure 2.9 Distribution of instantaneous delta phases (0.05–3 Hz) in the contralateral sensorimotor cortex at stimulus onset. Control subjects (A) and (B). PD patients (C) and (D). The light gray lines represent the individual subjects and the black lines are the group mean. Phase preference (entrainment) of delta is clearly visible from all phase distributions. Distributions of all individual subjects were aligned by centering the most preferred phase for each individual at π (two cycles are shown). (E) Group mean delta phase entrainment (error bars represent 1 SEM) as measured by the inter-trial coherence for both hemispheres and conditions, for control subjects and PD patients.

Phase entrainment of delta oscillations

As proposed by Lakatos et al. (2005), a rhythmic stream of stimuli will induce slow oscillations to align their high excitability phase with the occurrence of the stimuli. Therefore, the rhythmic task structure, with reaction stimuli occurring at a rate of 0.67 Hz, should allow for entrainment of slow oscillatory activity in the delta range (0.05–3Hz). The distribution of delta activity matched a source in sensorimotor cortex. To evaluate synchronization of delta activity, a virtual channel in the motor cortex of both hemispheres was created by means of spatial filtering using beam-forming techniques (see Methods). Delta band oscillations extracted from this virtual channel were entrained to the rhythm of stimulation as shown by the significant non-uniformity of phase at stimulus onset (Rayleigh's test with $P < 0.05$, for both groups, conditions and hemispheres). Instantaneous delta phases (aligned to the preferred phase for all subjects) at stimulus onset in the motor cortex contralateral to the response hand are shown in Figs. 2.9A–D and show clear non-uniformity of delta phase distributions for both conditions and groups.

The intertrial phase coherence (ITC), a measure of phase entrainment, was calculated for both groups, conditions and hemispheres separately and submitted to a mixed-design ANOVA. Entrainment was significantly stronger in the predictable than random condition, yielding a significant main effect of Predictability ($F(1,22) = 25.8$, $P < 0.0001$). There was a significant interaction between the factors Predictability and Hemisphere ($F(1,22) = 5.0$, $P < 0.04$), and this interaction was explained by a larger difference in entrainment between hemispheres in the predictable than in the random condition, as shown in Fig. 2.9E. There was a trend of entrainment being stronger in controls than in PD patients, as evidenced by a marginally significant main effect of Group ($F(1,22) = 4.1$, $P < 0.055$). In spite of the fact that the phase entrainment in the contralateral hemisphere in the predictable condition contributed most to this group difference, the three-way interaction Group by Predictability by

Hemisphere did not reach significance ($F(1,22) = 2.4$, $P = 0.11$).

Based on the concept of hierarchical coupling of different oscillations frequencies, we hypothesized that the amount of predictive beta modulation could be related to the delta ITC. Both measures showed a strong contralateral predominance in the predictable condition. We therefore evaluated the correlation between predictive beta modulation with delta phase ITC for all participants, for both hemispheres and conditions. In the predictable condition, entrainment of delta phase in the motor cortex was, across groups, significantly correlated with the cortical predictive beta modulation in the contralateral ($r = 0.42$, $P = 0.042$), but not in the ipsilateral hemisphere ($r = 0.23$, $P > 0.20$). In the random condition this correlation was, across groups, present in both the contralateral ($r = 0.41$, $P = 0.045$) and in the ipsilateral hemisphere ($r = 0.43$, $P = 0.026$) (see Figure S2.2). This pattern conforms to the Predictability by Hemisphere interaction that was found for delta ITC and for predictive beta modulation, and suggests a possible joint role in preparation and interlinked entrainment of delta and beta oscillations by the regular task structure.

2.4 Discussion

This study used a serial choice response task with a predictable task structure to investigate entrainment of oscillatory brain activity. A fast stimulus presentation rate, temporal predictability, and effector predictability invited advance preparation in an implicit fashion. The undemanding nature of the task resulted in an identical performance of PD patients and control subjects in terms of reaction time and error rate. Task-related beta-frequency oscillatory activity, however, showed a markedly different modulation profile in PD patients compared to control subjects. Associated changes in the delta frequency as well as the gamma frequency range suggest the relevance of hierarchical coupling between oscillations of different frequencies. The findings will be discussed in relation to the proposed prospective nature of beta power modulations, hierarchical coupling of oscillations, and gait rehabilitation based on entrainment with rhythmic cues.

Behavioural data

Task performance was identical in control subjects and patients, including the benefit gained from the alternating responses in the predictable condition. Hence both groups took advantage of effector predictability. That temporal predictability influenced performance as well, is suggested by the fact that perturbations of the fixed interval (the sequence-final deviant SOAs) caused an increase in reaction time in both groups, as a sign of entrainment. The larger RT-increment in the predictable than in the random condition can perhaps be explained by the further advanced preparation in this condition, incurring an added cost of temporal adjustment. The identical behavioural performance of PD patients and control subjects is a fortuitous circumstance, allowing differences in neurophysiological measures to be more reliably attributed to altered physiology.

Temporal dynamics of beta oscillations

There is increasing evidence for the relevance of excessive beta synchronization to the motor symptoms of PD. Key characteristics of beta power attenuation in the peri-movement time window are influenced by dopaminergic medication (Devos et al., 2006; Doyle et al., 2005a; Kühn et al., 2009) and by subthalamic nucleus (STN) stimulation (Giannicola et al., 2010; Kühn et al., 2008; Ray et al., 2008). Moreover, suppression of hypersynchronous beta activity, by medication or STN stimulation, is associated with improved motor performance (Devos et al., 2006; Doyle et al., 2005a; Kleiner-Fisman et al., 2003; Ray et al., 2008; Rodriguez-Oroz et al., 2005). Changes in beta activity resulting from dopaminergic medication and/or STN stimulation include an earlier onset of beta-ERD and larger amplitude of beta-ERD preceding and during a self-paced voluntary movement (Devos et al., 2003; Doyle et al., 2005a). The relevance of such observations is underscored by the fact that, in reaction time tasks, the onset of beta-ERD and beta power in the STN correlates with reaction time (Williams et al., 2005).

Of specific interest here, beta oscillatory power in PD is not only studied in the peri-movement time window, but also studied during the delay between a warning cue and an imperative signal (Oswal et al., 2012, 2013; Williams et al., 2003). Similar to the behaviour of beta activity at the cortical level (Androulidakis et al., 2007a; Gould et al., 2011; van Ede et al., 2011; Van Wijk et al., 2009), delay period beta power in the STN is modulated in an anticipatory fashion, based on the information provided by the cue and the anticipated response associated with the imperative signal. Like peri-movement beta activity, delay-period beta oscillatory power is influenced by dopaminergic medication, showing greater reactivity on medication (Oswal et al., 2012). These findings thus support that an important aspect of beta reactivity consists in the presetting of processing resources for future action (Jenkinson and Brown, 2011).

Whereas the above studies manipulated the information provided by the warning signal in an explicit way, our experimental paradigm influenced anticipatory activity in an implicit fashion. Firstly, the regular interval between reaction stimuli enabled temporal preparation and preparation of both response alternatives in the random condition. Secondly, the alternation of response sides in the predictable condition provided a salient but implicit cue to also prepare for the expected response side. Both manipulations produced the effects we expected. Across conditions, beta power started to reduce well before the next stimulus, yielding a preparatory beta-ERD. This preparatory ERD was larger and displayed a stronger ipsi-contralateral asymmetry in the predictable condition, due to effector selective preparation. Preparatory effects, expressed in the percentage of the beta-ERD occurring before stimulus presentation, were significantly smaller in PD patients than in control subjects. Importantly, the reduced preparatory beta-ERD was manifested as a main effect of Group, thus was not affected by whether the response side was predictable or not. This means that the reduced preparatory beta-ERD represents a deficit in predictive timing or reduced engagement of preparatory processes. Possibly as the result of a larger reactive ERD, the reduced predictive ERD in patients did not produce slower reaction times. The behavioural significance of predictive beta-

ERD is nevertheless upheld by the significant modulation by Predictability and by a significant correlation with reaction time.

In spite of existing evidence for a role of beta oscillations in predictive timing and anticipation of future actions (Arnal and Giraud, 2012; Jenkinson and Brown, 2011), one might ask whether the reduced prospective beta-ERD is not primarily due to a sluggish return to baseline or attenuated post-movement beta rebound in PD patients. This alternative account can be rejected for several reasons. Firstly, it is difficult to reconcile with the preserved modulation depth of beta power. Secondly, due to the especially pronounced lateralization of beta-ERS it predicts differences between the predictable and the random condition on the basis of trial repetition. Such an interaction of group by condition, for predictive beta-ERD, was not there. Thirdly, this account would predict that the deficit in predictive beta-ERD is ameliorated with longer intertrial intervals. A reanalysis of data from Praamstra and Pope (2007) (see Addendum) demonstrates that this is not the case. This reanalysis shows a robust deficit in predictive beta-ERD in patients, not recovering with longer intertrial intervals.

Temporal dynamics of gamma oscillations

Movement execution is accompanied by changes in the beta band, but there are also transient changes in gamma band (60–90 Hz) activity (for a review see Cheyne, 2013). An increase in gamma power (ERS) is usually seen in the primary motor cortex contralateral to the response hand during movement and this change in gamma power has a more focused spatial distribution than changes in beta power (Pfurtscheller et al., 2003). The observed gamma ERS is highly stable over time (Cheyne and Ferrari, 2013) and occurs irrespective of whether the movement is cued or self-paced (Muthukumaraswamy, 2010). Important here, gamma power can already increase prior to movement (Donner et al., 2009). Several studies have shown that gamma activity is also affected in PD, as they show reduced gamma power in rest (Stoffers et al., 2007), a more bilateral gamma ERS in STN LFPs (Androulidakis et al., 2007b), reduced gamma-mediated interregional coupling (Herz et al., 2014b), and an increased coupling between beta phase and gamma amplitude in the primary motor cortex (de Hemptinne et al., 2013). Reduced gamma power in PD can be restored using dopaminergic medication, and the increase in gamma power correlates with improvement in motor symptoms (Alegre et al., 2005; Androulidakis et al., 2007b; Devos et al., 2006; Litvak et al., 2012).

In line with the literature, we find a gamma ERS during movement execution in both conditions of the experiment. In the predictable condition this gamma ERS starts significantly earlier in control subjects than in PD patients, whereas in the random condition there is no difference in onset between groups. Interestingly, the temporal profile of gamma power is very similar to the temporal profile of the beta power changes, as shown in Fig. 2.8. This similarity in temporal profile combined with the significant differences in onset times lends further support to the interpretation that PD patients do not engage in a prospective processing mode. The recent suggestion of coupling between beta and gamma oscillations (de Hemptinne et al., 2013) could also be relevant for the closely matched time courses in our data.

The matched time courses of gamma-ERS and beta-ERD are also reminiscent of the reciprocal relationship between gamma and beta LFP power in the STN region (Fogelson et al., 2005).

Entrainment of delta oscillations in motor cortex

The use of a fixed temporal interval between stimuli in the current study enables slow oscillatory activity in the delta band (0.05–3 Hz) to entrain to the stimulus rhythm, in the form of phase resetting of slow oscillations to external events. The entrainment of slow oscillations may serve the purpose of bringing relevant brain structures into an optimal state for processing the stimuli to which they synchronize (Lakatos et al., 2008; Schroeder and Lakatos, 2009) and can occur not only in the sensory cortices but also in the frontal, parietal and central areas of the cortex (Besle et al., 2011). Several studies have shown that entrainment is beneficial for stimulus processing as it leads to enhanced sensitivity to (near-threshold) sensory stimuli (Cravo et al., 2013; Henry and Obleser, 2012; Monto et al., 2008; Saleh et al., 2010), can suppress distracting stimuli (Gomez-Ramirez et al., 2011; Schroeder and Lakatos, 2009), and lead to faster reaction times (Stefanics et al., 2010).

In this study we find entrainment of delta oscillations in the motor cortex, measured by phase consistency over trials. In the random condition the entrainment is, as expected, equal for both hemispheres. Since the upcoming response side is unpredictable in this condition, both hemispheres need to be brought into an optimal state for stimulus processing and response preparation. In the predictable condition, however, there was significantly more entrainment in the hemisphere contralateral to the response hand than in the ipsilateral hemisphere, suggesting that participants make use of the implicit effector predictability. The same Predictability by Hemisphere interaction characterized the predictive beta modulation. Previous work has indeed shown hierarchical coupling between oscillations of different frequencies, for example between delta phase and theta power (Lakatos et al., 2005), theta phase and beta power (Cravo et al., 2011) or theta phase and gamma power (Canolty et al., 2006). We hypothesized that delta phase might be related to beta amplitude and that stronger entrainment of delta oscillations would lead to higher motor readiness, reflected in lower beta power. This was confirmed by the computed correlation between predictive beta modulation and pre-stimulus delta phase entrainment. The obtained correlation is in line with results of Saleh et al. (2010), who suggested that delta phase and beta amplitude work together to enhance sensitivity to predictable and task-relevant visual cues.

Recently it has been suggested that the contingent negative variation (CNV) actually might reflect entrained delta oscillations (Besle et al., 2011; Lakatos et al., 2013b), a proposition strongly supported by data in Stefanics et al. (2010). If this is the case, the tendency to reduced entrainment of delta oscillations that we find here is in line with earlier findings regarding the CNV in PD. Previous studies show that the CNV is reduced or absent in PD patients during implicit timing tasks (Cunnington et al., 1995; Praamstra and Pope, 2007), but not when PD patients are explicitly instructed to take advantage of the predictable timing of reaction stimuli (Cunnington et al., 1999). While we considered that the predictable condition in the

present study might have a similar effect as explicit instruction (see Introduction), this was clearly not the case, neither for delta ITC nor for predictive beta modulation. Our data thus add to growing evidence for lack of spontaneous entrainment in PD. An interesting early piece of evidence is the observation that the CNV is even more affected in PD than the readiness potential, recorded with self-paced movements (Ikeda et al., 1997).

Rhythmic cueing and entrainment of oscillatory activity

Although our study used upper limb responses, the results have relevance to cueing in PD. There are numerous reports that rhythmic cueing improves gait in Parkinson's disease (Morris et al., 1996a; Nieuwboer et al., 2007; Rochester et al., 2009; Thaut et al., 1996; van Wegen et al., 2006; Willems et al., 2006; for review see Nombela et al., 2013), but rhythmic cues can also improve upper limb movements (Vercruysse et al., 2012). The underlying mechanisms of cueing are not clear, however. The most explicit views hold that external cues facilitate movement on the basis of a recruitment of lateral premotor areas compensating for deficient activation of the medial premotor cortex, effectively bypassing basal ganglia–medial premotor cortex circuits (Cunnington et al., 1995; Rochester et al., 2007). This view does not have strong support. A recent meta-analysis of functional imaging studies in PD showed that neither increased lateral nor decreased medial activation are consistent findings (Herz et al., 2014a). Neuroimaging studies in healthy human subjects do also not support a strong segregation between brain activations associated with internally vs. externally cued movements (Ballanger et al., 2006; Cunnington et al., 2002; Jahanshahi et al., 1995; but see Debaere et al., 2003). Finally, cell recordings in the basal ganglia of primates do not reveal selective involvement of the basal ganglia in internally generated movements (Mink and Thach, 1991; Turner and Anderson, 2005).

Recent fMRI work on rhythm perception by Grahn and Rowe (2009), further corrects the above view on two counts. These studies demonstrated that the lateral premotor cortex and the putamen are preferentially activated by rhythms with a strong beat, and that the activation serves the prediction of beat timing in a sequence of stimuli. Hence, if rhythmic cueing relies on the lateral premotor cortex, then this route is not likely to "bypass the basal ganglia", and serves moreover a predictive mode of motor activation instead of the presumed reactive mode. It has been pointed out already that these data, in fact, raise an important paradox, because if rhythm perception depends on the basal ganglia, how can rhythm improve movement in PD patients (Chen et al., 2009; Nombela et al., 2013)?

The present data reinforce this paradox by the demonstration of oscillatory entrainment with beta-ERD occurring predominantly before reaction stimuli (predictive beta-ERD) in healthy control subjects, contrasting with an entrainment pattern of predominantly reactive beta-ERD in PD patients. This finding suggests that if repetitive external stimulation supports movement in PD, it does not do so by recruiting a control system that is left unaffected by the disease. Nor can it be claimed that it invokes a more automatic mode of activation (Nombela et al., 2013). Note that the data do not discount the possibility that rhythmic cues can

be beneficial. A salient aspect of both current data and previous data acquired in a similar paradigm (Praamstra and Pope, 2007) is the preserved depth of the beta power modulation in PD patients, achieved through a higher reactive beta-ERD. This contrasts with the commonly reported reduction of beta ERD and ERS in PD (Degardin et al., 2009; Devos et al., 2003; Doyle et al., 2005a; Heinrichs-Graham et al., 2013; Oswal et al., 2012; Pfurtscheller et al., 1998). In combination with PD patients' normal reaction times, this raises the interesting possibility that facilitatory effects of rhythmic or repetitive stimuli in PD are mediated by an enhancement of beta modulation depth.

Conclusion

Abnormal beta oscillatory activity in basal ganglia–cortical circuits is a known biomarker of PD, with possible pathophysiological significance. We report several new findings with respect to beta activity in PD. The observed shift from a prospective to a reactive modulation of beta power supports the notion that dynamic modulation of beta oscillatory power serves a predictive function (Jenkinson and Brown, 2011; Oswal et al., 2012) and that it is precisely this function which is compromised in PD. We further establish a correlation between predictive beta modulation and phase synchronization of slow delta oscillations. This correlation fits the emerging concept of hierarchical coupling between different oscillation frequencies (Lakatos et al., 2005; Schroeder and Lakatos, 2009), also supported, albeit weaker, by the similarity in time course of beta-desynchronization and gamma-synchronization. The concept of hierarchical oscillatory coupling entails a possible link between the known attenuation of slow brain potentials in PD (Cunnington et al., 1995; Jahanshahi et al., 1995; Praamstra et al., 1996a, 1996b; Praamstra and Pope, 2007; Wascher et al., 1997) and abnormal beta and gamma oscillatory synchrony. It is important to note, however, that the here presented evidence is merely correlational. What also needs further investigation is why predictive beta modulation in PD, the reduction of which indicates a deficit in predictive timing or reduced engagement of preparatory processes, remains sensitive to effector predictability, corresponding with a preserved behavioural benefit. Possibly, the normal performance of patients is not just due to the non-demanding nature of the task, but the result of reduced predictive beta-ERD being compensated by increased reactive beta-ERD, enabled by the rhythmic task structure. If that is the case, the conclusion is warranted that entrainment fails to engender the same predictive mode of motor activation in PD patients as in healthy controls, but that there is still a performance-enhancing effect of entrainment.

2.5 Addendum

For the purpose of comparison with the data of the present paper, beta power modulation in Praamstra and Pope (2007) was reanalyzed. The reanalysis concerned the differentiation of beta-ERD in a predictive and a reactive component, by means of the index described in the Methods. We refer to the original paper for further information concerning the participants (10 PD patients, 12 control subjects), task and EEG data acquisition and analysis. In contrast to the present experiment, the task had two different SOA lengths of 1500 and 2000 ms. There was no manipulation of effector (choice) predictability. Beta power values were measured from symmetrical ROIs, each consisting of five electrodes, overlying the left and right motor cortices.

Across groups, the modulation depth of beta power was influenced solely by Hemisphere, being of higher amplitude contra- than ipsilateral to the side of movement ($F(1,20) = 17.2$, $P < 0.0001$). There was no between groups difference in modulation depth ($F(1,20) < 1$).

Predictive modulation of beta power was higher with long than with short SOAs ($F(1,20) = 32.0$, $P < 0.0001$). Between groups, predictive beta modulation was considerably smaller for patients, as shown in Table 2.2, resulting in a significant effect of Group ($F(1,20) = 9.5$, $P < 0.006$). There were no interactions involving the factor Group.

Table 2.2 Predictive beta modulation in the study of Praamstra and Pope (2007). Long and short SOAs refer to intervals of 2000 and 1500 ms respectively.

Condition and Hemisphere	*Control subjects (% ± 1 SD)*	*PD patients (% ± 1 SD)*
Long SOA contralateral	59 ± 16	35 ± 18
Long SOA ipsilateral	58 ± 21	34 ± 18
Short SOA contralateral	45 ± 19	25 ± 18
Short SOA ipsilateral	45 ± 21	22 ± 19

2.6 Supplementary Figures

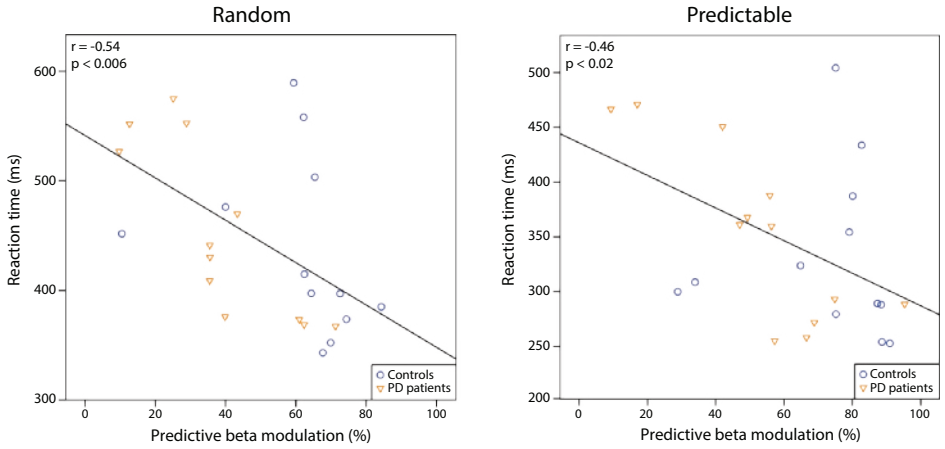

Figure S2.1 Correlation between reaction time and the percentage of predictive beta modulation in the hemisphere contralateral to the response hand, for the random (left panel) and the predictable (right panel) conditions.

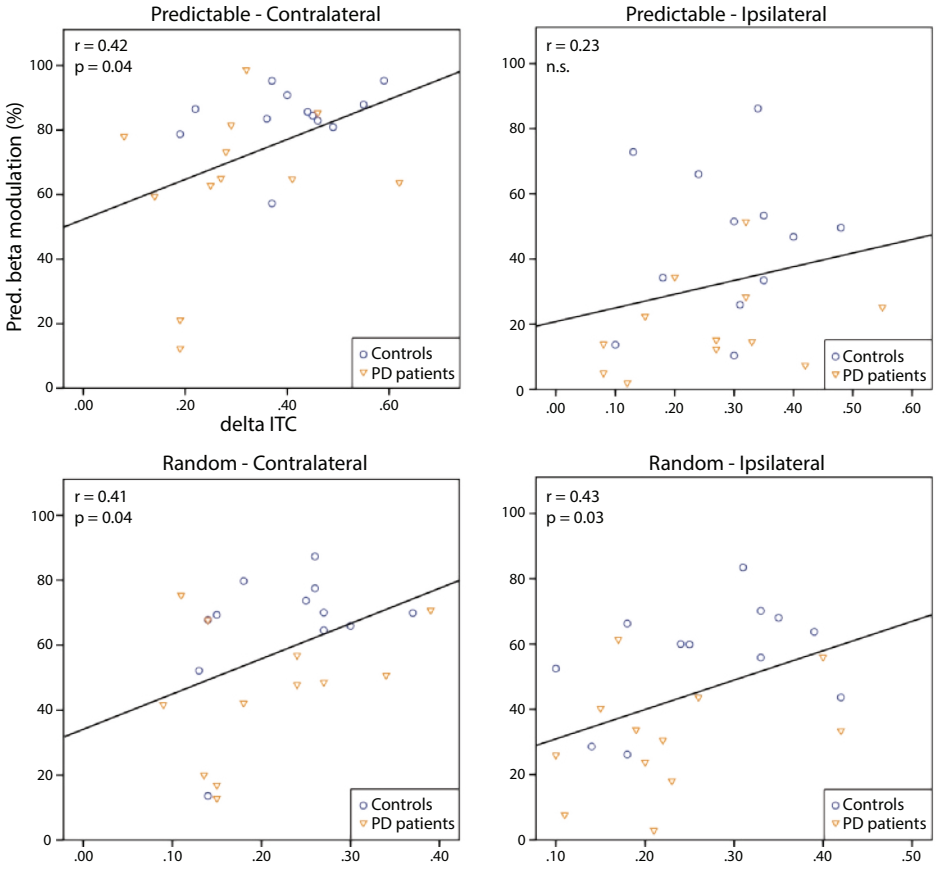

Figure S2.2 Correlations between the percentage of predictive beta modulation and the amount of delta phase synchronization, in both conditions and hemispheres.

Effects of rhythmic stimulus presentation on oscillatory brain activity: the physiology of cueing in Parkinson's disease

Adapted from
Effects of rhythmic stimulus presentation on oscillatory brain activity: the physiology of cueing in Parkinson's disease.
te Woerd E.S., Oostenveld R., Bloem B.R., de Lange F.P., Praamstra P. (2015) Neuroimage: Clinical: 9: 300-309

3

Abstract

The basal ganglia play an important role in beat perception and patients with Parkinson's disease (PD) are impaired in perception of beat-based rhythms. Rhythmic cues are nonetheless beneficial in gait rehabilitation, raising the question how rhythm improves movement in PD. We addressed this question with magnetoencephalography recordings during a choice response task with rhythmic and non-rhythmic modes of stimulus presentation. Analyses focused on (i) entrainment of slow oscillations, (ii) the depth of beta power modulation, and (iii) whether a gain in modulation depth of beta power, due to rhythmicity, is of predictive or reactive nature. The results show weaker phase synchronisation of slow oscillations and a relative shift from predictive to reactive movement-related beta suppression in PD. Nonetheless, rhythmic stimulus presentation increased beta modulation depth to the same extent in patients and controls. Critically, this gain selectively increased the predictive and not reactive movement-related beta power suppression. Operation of a predictive mechanism, induced by rhythmic stimulation, was corroborated by a sensory gating effect in the sensorimotor cortex. The predictive mode of cue utilization points to facilitation of basal ganglia-premotor interactions, contrasting with the popular view that rhythmic stimulation confers a special advantage in PD, based on recruitment of alternative pathways.

3.1 Introduction

There is evidence that rhythmic cues can improve gait in patients with Parkinson's disease (PD) (for review see Keus et al., 2007; Nombela et al., 2013; Spaulding et al., 2013). Recent studies, however, have shown that PD patients are impaired in rhythm perception, especially of beat-based rhythms with strong temporal regularity (Grahn and Brett, 2009). This deficit might have its basis in the involvement of the basal ganglia in rhythm perception and production, as suggested by neuroimaging studies (Grahn and Rowe, 2009, 2013) and by neural recordings in monkey basal ganglia (Bartolo et al., 2014; Bartolo and Merchant, 2015; Merchant et al., 2015). The impairment in rhythm perception and its presumed basis in basal ganglia dysfunction raise the question how rhythm can improve movement in PD patients (Chen et al., 2009; Nombela et al., 2013; te Woerd et al., 2014).

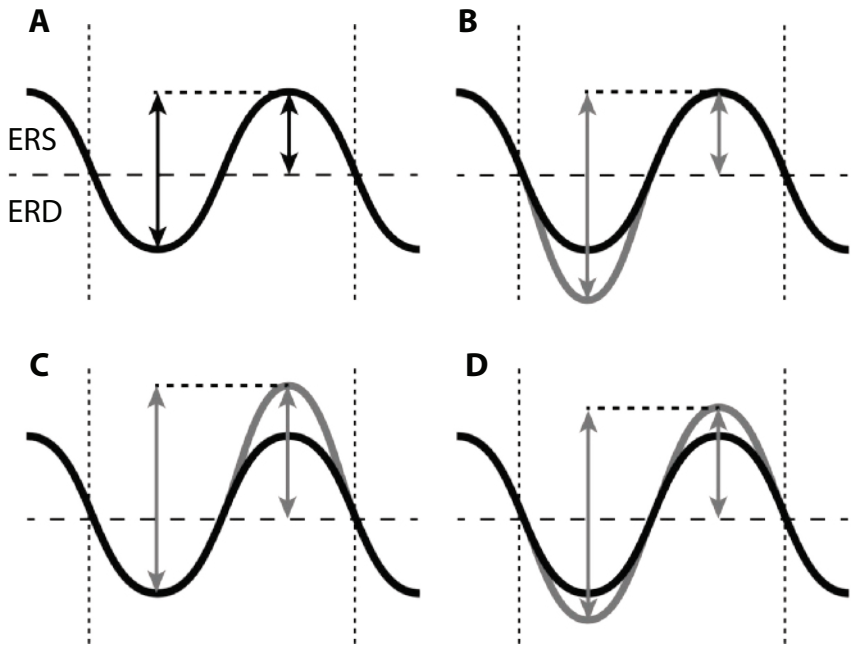

Figure 3.1 Possible outcome scenarios of changes in beta power modulation as a result of rhythmic vs. non-rhythmic stimulus presentation. (A) Typical time course of beta power in a serial reaction task with stimuli presented at time points indicated by vertical lines. A decrease of beta power relative to baseline is called event-related desynchronisation (ERD). An increase of power is called event-related synchronisation (ERS). Movement preparation and execution is accompanied by a beta ERD (movement-related beta suppression). This suppression can be divided in a predictive and a reactive part. Predictive beta suppression is calculated as the power change from pre-stimulus ERS-peak to stimulus-onset (shown by the right arrow in A) relative to the modulation depth (from pre-stimulus ERS-peak to subsequent ERD-trough; left arrow in A). Rhythmic stimulus presentation is expected to increase the beta modulation depth. (B) This increase might be mediated by a stronger desynchronisation, producing higher amplitude reactive beta suppression. (C) Alternatively, it might be mediated by a stronger synchronisation, indicating a predictive mode of cue utilization and yielding higher predictive beta suppression. (D) An increase in beta modulation may also consist of increased synchronisation and desynchronisation phases.

An important element of the recent evidence for basal ganglia involvement in rhythm perception is that putaminal activity and associated putamen – premotor interaction during rhythm perception are engaged in a predictive fashion (Grahn and Rowe, 2009, 2013; Merchant et al., 2015). Notably, relevant putamen-premotor

interactions include interactions with the supplementary motor area but also with the lateral premotor cortex. The predictive engagement of putamen – lateral premotor cortex circuits by rhythm processing underscores the significance of the question how rhythm improves movement in PD. This is because this predictive engagement contradicts the popular view that the lateral premotor cortex supports compensation in PD due to a mode of processing that is more externally driven than requiring internal generation and prediction (Cunnington et al., 1995, 2001; Debaere et al., 2003; Jahanshahi et al., 1995; Sabatini et al., 2000; Samuel et al., 1997; Vercruysse et al., 2012).

To investigate the physiological basis of rhythmic stimulation benefits in PD, we recorded movement-related brain activity during a choice response task with rhythmic and non-rhythmic modes of stimulus presentation, using magnetoencephalography (MEG) in 15 PD patients and 15 control subjects. There is increasing recognition that brain oscillations tend to entrain to environmental regularities and that this physiological mechanism may underlie behavioural advantages conferred by such regularities (Schroeder and Lakatos, 2009). Hence we analysed slow brain oscillations in the frequency range of the stimulus presentation rate. Of key interest was, furthermore, the response of the sensorimotor beta rhythm, which is a known pathophysiological marker of PD (e.g. Brittain and Brown, 2014; Gatev et al., 2006; Hammond et al., 2007; Pollok et al., 2012), and which is hypothesized to represent an internal likelihood index for pending voluntary action (Engel and Fries, 2010; Jenkinson and Brown, 2011). The magnitude of the movement-related beta amplitude modulation, commonly attenuated in PD (e.g. Devos et al., 2003b; Doyle et al., 2005; Heinrichs-Graham et al., 2014), was expected to demonstrate a gain with rhythmic stimulus presentation. Crucially, to evaluate whether such a gain is due to the adoption of a more predictive mode of control, as opposed to reactive responding, movement-related beta suppression was separated into a predictive and a reactive phase, occurring before and after a reaction stimulus, respectively (Praamstra and Pope, 2007; te Woerd et al., 2014). Figure 3.1 outlines the different outcome scenarios based on this distinction.

3.2 Materials and methods

Participants

Participants were 15 PD patients (10 men; aged 61 ±5years) and 15 healthy subjects (9 men; aged 61 ±5 years). Control subjects were without history of neurological or psychiatric disease. PD patients were of mild to moderate disease severity (see Table 3.1). Participation was based on informed consent according to the Declaration of Helsinki and the study was approved by the local ethics committee (CMO Arnhem-Nijmegen). All patients were on dopaminergic medication and had a mean score of 28 (±7) on the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS) (see Table 3.1). The investigation and UPDRS rating were performed in the morning, after overnight withdrawal of medication (>12 h).

Table 3.1 Demographic and clinical characteristics of participating Parkinson patients. UPDRS motor score was determined directly after the experiment. Levodopa was always used with a dopadecarboxylase inhibitor.

Subject number	*Age (yrs) and gender*	*Years since diagnosis*	*Most affected side*	*UPDRS motor score*	*Dominant hand*	*Medication (daily dose)*
1	66, M	13	R	37	R	Levodopa 1000 mg Entacapone 800 mg Pramipexol 1 mg
2	63, M	10	R	30	R	Levodopa 700 mg
3	66, M	6	L	40	R	Levodopa 700 mg Pramipexol 1.125 mg
4	56, M	3	R	22	R	Levodopa 300 mg
5	53, M	2	L	27	R	Levodopa 700 mg
6	61, M	14	R	24	L	Levodopa 500 mg Pramipexol 3.75 mg
7	54, F	6	R	33	R	Levodopa 800 mg
8	68, F	15	L	30	R	Levodopa 850 mg Pramipexol 3.75 mg Amantadine 200 mg
9	63, F	5	L	14	R	Levodopa 600 mg Pramipexol 1.5 mg
10	66, M	2	L	22	R	Levodopa 300mg
11	55, F	4	L	25	R	Levodopa 600 mg Pramipexol 0.375 mg
12	56, M	7	R	33	R	Levodopa 500 mg
13	69, M	5	L	25	R	Levodopa 300 mg Pramipexol 1.125 mg
14	58, F	7	L	19	R	Levodopa 300mg Ropinirol 6 mg Selegiline 10 mg Amantadine 200 mg
15	62, M	6	R	32	L	Levodopa 900 mg Entacapone 800 mg Ropinirol 2 mg Amantadine 200 mg
Mean (±SD)	61 ± 5	7 ± 4		28 ± 7		

Task and procedure

The experiment consisted of a serial choice response task to arrow stimuli presented on a screen, with the response being an index or middle finger button press, depending on the direction of the arrow. The ordering of left and rightward arrows was always random. The critical experimental manipulation concerned the temporal predictability of successive stimuli, which was manipulated by using two types of blocks. In one version (the "rhythmic" condition), the SOA (stimulus onset asynchrony) between successive stimuli was always 1.5 s. In the other version (the "non-rhythmic" condition), the SOA between successive stimuli varied between 1 and 2 s (in 0.1 s steps, with the majority being 1.5 s (~40%)). Subjects used one hand during each block, starting the first block with their dominant hand and switching to the other hand for the next block. Half the subjects started with the rhythmic, the other half with the non-rhythmic condition. Rhythmicity was alternated every two blocks, such that all subjects first performed one condition with both hands before switching to the other condition.

The experiment was divided in eight blocks of ~5 min each, containing 160 stimuli per block. Each block was preceded by a 20 s resting period during which ongoing brain activity was recorded. In order to make an unbiased comparison between conditions, only the 1.5 s intervals from the non-rhythmic condition were used for analyses and an equal number of stimuli from the rhythmic condition. The experiment was preceded by a short practice block and participants were instructed to press the correct button as swift as possible, and were not made aware of the rhythmicity manipulation. Stimuli were presented with Presentation 14.9 software (Neurobehavioural Systems), using a liquid crystal display video projector, and back-projected onto a translucent screen in the magnetically shielded room. Participants were seated in the MEG-chair with their eyes 75 cm from the screen, and response pads attached to the armrests of the chair. Stimuli were presented in white on a grey background for 300 ms. The fixation area was permanently indicated by white brackets surrounding the central screen area where the arrow stimuli were presented. The brackets enclosed a square of 7.2° × 6.1° of visual angle; the arrows measured 1.2° × 1.2° of visual angle.

MEG recordings

Ongoing brain activity was recorded using a whole-head MEG system with 275 axial gradiometers (VSM/CTF Systems, Coquitlam, BC) in a magnetically shielded room. During the experiment, we continuously measured head position relative to the sensor array using localization coils that were placed at the nasion and in the left and right ear canals. Vertical electro-oculogram (EOG) was recorded from the supra- and infraorbital ridges of the left eye, and horizontal EOG from the bilateral canthi. MEG and EOG data were sampled at 1200 Hz.

Behavioural analyses

Reaction time analyses were performed on the responses to the visual cues. We excluded trials with erroneous responses and discarded trials in which the response was too slow (N900 ms). Mean response times were determined for each condition separately. Differences in reaction time variability, at the individual subject level, were determined by using the coefficient of variation (ratio of standard deviation to the mean response time). As musical training could influence the experimental outcomes (Grahn and Rowe, 2009), all subjects filled out the subpart 'musical training' of the Goldsmiths Musical Sophistication Index (v1.0) (Müllensiefen et al., 2014). All correlations between reaction time and other behavioural or neurophysiological markers are calculated by means of a (parametric) Pearson correlation, and are listed with uncorrected p-values. However, if a correlation does not survive a Bonferroni correction for multiple comparisons, this is explicitly mentioned.

MEG data preprocessing

MEG data were analysed with MATLAB (2011b) (Mathworks, Natick, MA) using the open-source FieldTrip toolbox (Oostenveld et al., 2011). For the main analyses, epochs of 5000 ms (3000 ms pre-stimulus and 2000 ms post-stimulus) were extracted from the continuous data separately for both task conditions and response sides. After removal of trials containing muscle artifacts, slow drift, or SQUID (superconducting quantum interference device) jumps, data were down-sampled to 600 Hz. Independent component analysis was used to remove any remaining variance caused by eye blinks and heartbeat artifacts. As an extra check, the remaining data epochs were visually inspected and any remaining epochs with artifacts were removed manually. The remaining stimulus-locked epochs were submitted to time-frequency and statistical analyses. For more details about the preprocessing, we refer to Te Woerd et al. (2014). All statistical analyses presented here were performed using SPSS version 19 (IBM Corp. Armonk, NY) unless stated otherwise.

MEG analyses

Beta activity

Since beta oscillatory activity (13–30 Hz) is most prominent in the sensorimotor system, and lateralizes with unimanual responses, sensorimotor regions of interest (ROI) were determined by a subtraction (across conditions and groups) of beta activity associated with the left and right hand responses. Subsequently, the 25 channels with strongest beta modulation above each hemisphere were selected and those without a homologous sensor over the opposite hemisphere rejected. This resulted in two symmetric ROIs overlying the sensorimotor cortices with 19 sensors each.

Differences in oscillatory power in the ROIs between conditions were investigated by means of cluster-based non-parametric permutation tests (Maris and Oostenveld, 2007) in FieldTrip. To study beta power changes over time, power values were

averaged over the entire beta band and all sensors per ROI, creating contra- and ipsilateral time series of beta power. Time series for the left and right hand response conditions were combined by averaging the conditions separately for the contra- and the ipsilateral hemisphere. Modulation depth of beta power was defined as the difference between maximum pre-stimulus ERS and subsequent ERD trough. The amount of predictive beta modulation was defined as the change in beta power from maximum pre-stimulus ERS to the time of stimulus onset, relative to the modulation depth. The baseline against which beta power changes were measured was defined by the mean power of the analysis epoch, effectively the same as the mean power across the whole measurement session (Tan et al., 2014a). The results were verified with an alternative baseline, i.e., the resting power before the start of experimental blocks.

Delta activity

For the analyses of delta phase entrainment, the source of beta activity was identified using frequency-domain beam-forming source estimation (Gross et al., 2001). We contrasted the beta ERD with the beta ERS activity using two 500 ms time windows centered on the time points of maximal post-stimulus ERD and ERS. As the beam-former input required only one frequency, we used the 20 Hz frequency (resulting in 10 full cycles per time window). A realistic single-shell head model (Nolte, 2003) was created for all individuals using the brain surface from their individual segmented MRI (if available) or an MNI template-MRI (Holmes et al., 1998). The brain volume of each individual was discretized to a grid with a 10 mm resolution and the lead field matrix was calculated for each grid point according to the head position in the system and the forward model. A spatial filter was then constructed for each grid point using the covariance and lead field matrices. Source strengths were calculated for the ERD and ERS windows, after which these were contrasted and the location coordinates of maximal difference were saved. Delta phase analyses were performed on spatially filtered data using a time-domain beam-former source estimation (Van Veen et al., 1997). This beam-forming spatial filter for the stored location of interest (the contralateral motor cortex) was used to filter the MEG data. The LCMV spatial filter passed the activity at the location of interest with unit-gain, while optimally suppressing all other noise and source contributions to the MEG data. To allow the estimation of phase at low frequencies, we expanded each data epoch with mirror (time-reversed) images of itself. This procedure increased the length of each epoch to ~16.7 s (resulting in a ~0.067 Hz frequency resolution) while preserving data continuity (Cohen, 2014). The strength of phase preference was acquired by calculating the intertrial phase coherence (ITPC) over all trials within each individual in the frequency range 0.13–10 Hz. Evoked power was investigated by averaging all epochs and submitting the averaged epoch to time frequency analysis using a single Hanning taper and an adaptive window of three cycles for each frequency in the range 0.13–10 Hz. As a strong ITPC at the task rhythm (~0.67 Hz) could also be caused by evoked activity from stimulus presentation, we calculated the power of evoked activity at 0.67 Hz for all subjects and conditions and used a repeated measures ANOVA to test for differences between conditions and groups. For the analysis of instantaneous phase, all epochs were band-pass

filtered between 0.05 and 3 Hz using a finite impulse response least squares filter. Phase values were calculated using the Hilbert transform of the band-pass filtered data. To test if any phase preference was present at stimulus onset, Rayleigh's test for uniformity of phase data was used (Fisher, 1993). Rayleigh's test and ITC calculations were performed using the MATLAB circular statistics toolbox (Berens, 2009).

3.3 Results

Behavioural data

Participants had to respond as fast as possible to arrow stimuli presented on screen. Mean response times to all intervals were faster in the rhythmic than non-rhythmic condition (controls: 401 ± 49 ms vs 422 ± 43 ms; PD patients: 460 ± 82 ms vs 486 ± 81ms), yielding a significant main effect of Rhythmicity ($F(1,28) = 45.6$, $P < 0.0001$) (see Fig. 3.2). Mean response times of control subjects were faster than those of PD patients, as indicated by a main effect of Group ($F1,28 = 6.6$, $P = 0.016$). However, both groups benefitted equally from rhythmicity, as there was no interaction between Rhythmicity and Group ($F(1,28) < 1$). The amount of musical training was not different between groups ($F(1,28) = 1.4$, $P = 0.25$), and did not correlate with reaction time benefit ($r = 0.11$, $P = 0.55$).

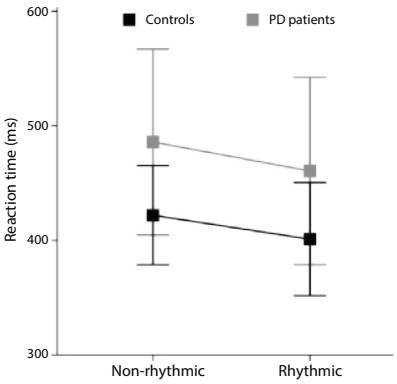

Figure 3.2 Group mean response times for both groups in the non-rhythmic and rhythmic conditions. Error bars represent 1 standard deviation, and all reaction times are averaged over left and right hand responses.

Oscillatory brain activity

Phase entrainment of delta oscillations

Since the rhythmic stimuli allow for entrainment of slow oscillations, we analysed phase synchronisation in the delta band (0.05–3 Hz) using a virtual channel located in the contralateral motor cortex. Oscillatory delta-band activity was entrained to the reaction stimuli as shown by analyses of phase-consistency over trials (Fig. 3.3). Delta-band oscillations showed a significant phase preference at stimulus onset (Rayleigh's test for non-uniformity with $P < 0.05$, for both groups and conditions). The instantaneous phases of delta at stimulus onset (aligned to the preferred phase for all subjects) in the motor cortex are shown in Figure 3.3A. Phase synchrony was significantly stronger (as represented by the modulus length, Fig. 3.3D) in the rhythmic than non-rhythmic condition, yielding a main effect of Rhythmicity ($F(1,28) = 6.7$, $P = 0.015$). Overall, phase synchrony was stronger in healthy controls than PD patients ($F(1,28) = 7.8$, $P = 0.009$), but there was no interaction between the factors Rhythmicity and Group. The strength of delta phase synchrony correlated with response speed, but only in the rhythmic ($r = –0.41$, $P = 0.024$; uncorrected

p-value, does not survive multiple comparison correction) and not in the non-rhythmic condition ($r = -0.21$, $P = 0.27$), supporting a behavioural benefit of entrainment of slow oscillations in conditions of rhythmic stimulus presentation, that is absent with non-rhythmic presentation (cf. Cravo et al., 2013).

Relevant to the interpretation of phase synchrony is whether it is due to alignment of endogenous slow oscillations as opposed to a stimulus-evoked effect. The fact that there was no increase in power at the task rhythm (0.67 Hz) (Fig. 3.3C), suggests that the strong ITPC values at this frequency (Fig. 3.3B) reflect the entrainment of endogenous oscillations. This is supported by the fact that evoked power (at the task rhythm) at stimulus onset was stronger in the non-rhythmic than rhythmic condition for both groups ($F(1,28) = 28.2$, $P < 0.001$) (Fig. 3.3F), while the ITPC effect showed a trend in the opposite direction ($F(1,28) = 3.1$, $P = 0.09$) (Fig. 3.3E). Together, these results show that phase synchronisation across conditions was weaker in patients than in controls. Entrainment, i.e., elevated phase synchronisation with rhythmic stimulus presentation, was the same in both groups. The behavioural relevance of this entrainment was supported by a correlation with reaction time.

Distribution of sensorimotor beta activity

Time-frequency analyses of data from the ROI-sensors showed predominant movement-related modulations in the beta band. We first evaluated the distribution of the beta modulation, by quantifying beta power peak-to-peak from maximum desynchronisation to subsequent maximum synchronisation. The modulation of beta activity was maximal over the motor cortex contralateral to the response hand, as seen in Figure 3.4.

As shown in the time-frequency plots of Figure 3.5, the modulation of beta power occurred over the full beta range from 13 to 30 Hz. The beta modulation followed a fixed pattern, with a reduction in beta power before and during movement, and a subsequent increase in beta power shortly after movement termination. These power changes were, for both groups, stronger in the rhythmic than non-rhythmic condition, as shown by two clusters of stronger desynchronisation and one of synchronisation ($P < 0.032$ for all clusters).

Rhythmicity and beta modulation depth

The modulation depth was significantly larger in the rhythmic than in the non-rhythmic condition ($F(1,28) = 25.0$, $P < 0.0001$), and was larger in the hemisphere contralateral than ipsilateral to the response hand, for both groups ($F(1,28) = 153.3$, $P < 0.0001$) (see Fig. 3.6A-B). More importantly, there was no interaction between Group and Rhythmicity ($F(1,28) < 1$). This means that the increase in modulation depth was equal for both groups. Also, in both groups, the increase in modulation depth was solely caused by a stronger ERS phase (as shown by the difference between conditions in Fig. 3.5), with similar spatial distribution for both groups (Fig. 3.6D).

Figures 3.5 and 3.6 show an apparent reduction in modulation depth in PD patients, but there was not a significant difference between groups ($F1,28= 2.2$, $P = 0.15$). The apparent difference between the group averages could be due to greater variability in reaction times in the patient compared to the control group, leading to poorer

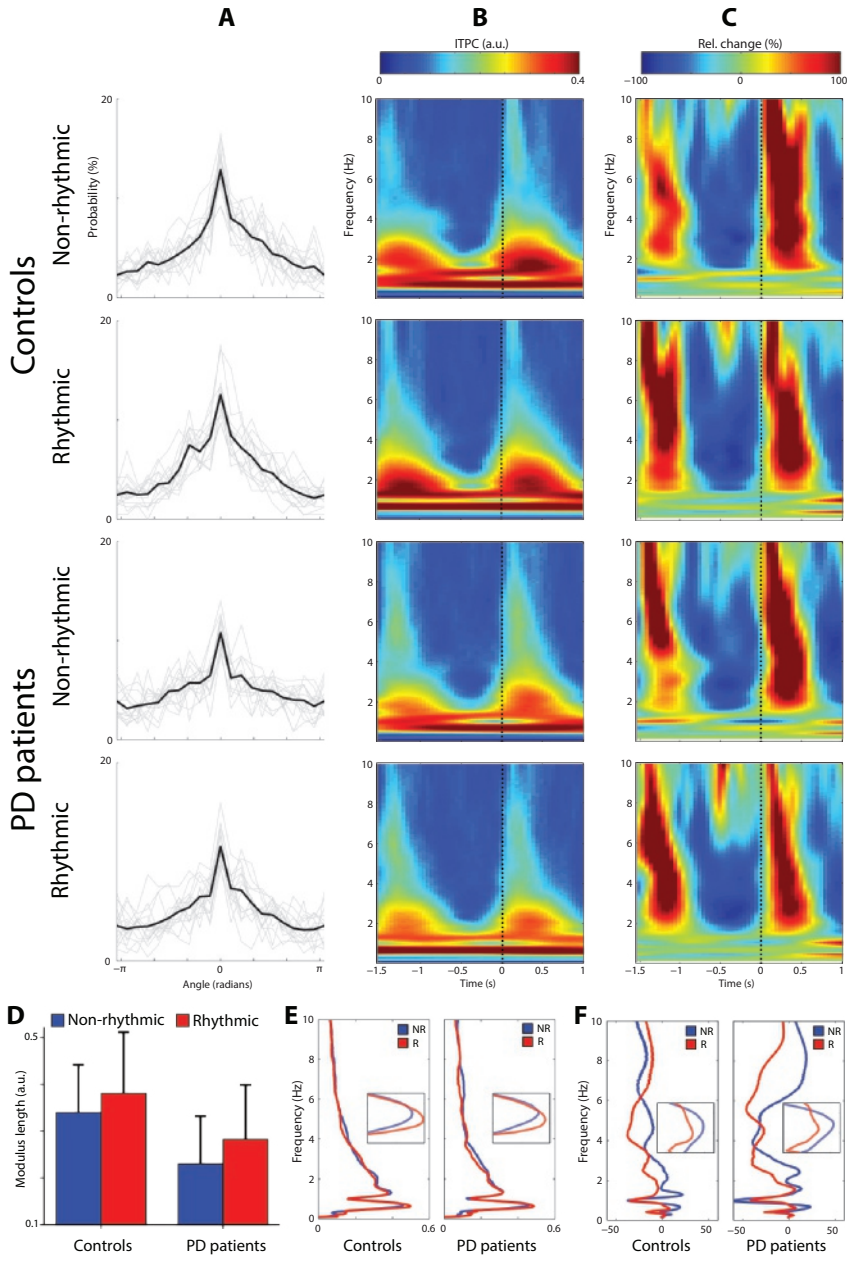

Figure 3.3 Phase entrainment analyses in a virtual channel located in the motor cortex contralateral to the response hand (all results are averaged over all trials and response hands). (A) Distributions of instantaneous delta phase at stimulus onset (aligned to the preferred phase of each subject). The light grey traces show all individual subjects, and the black traces are the group means. Intertrial phase coherence (ITPC) values (B) and evoked (ERF) power (C) are shown for both groups and conditions. (D) Overview of modulus lengths resulting from the phase distributions in (A) for both groups and conditions. ITPC values (E) and evoked power (F) at stimulus onset for both conditions (non-rhythmic in blue, rhythmic in red) and groups (controls in left panel and PD patients in right panel). Insets show the ITPC and evoked power around the stimulation frequency (0.67 Hz) at stimulus onset.

alignment of ERD and ERS phases. This mechanism cannot explain the between-conditions effect, as reaction time variability was similar between conditions. The difference between rhythmic and non-rhythmic condition can neither be explained by a difference in reaction time variability (between conditions) at the individual subject level. This was established by computing for each subject and condition the coefficient of variation. A Group by Rhythmicity analysis of this coefficient revealed no significant difference between groups ($F(1,28) = 1.7$, $P = 0.20$), nor a difference between conditions ($F(1,28) = 1.8$, $P = 0.19$).

To rule out any effects due to the choice of baseline, the same analyses were repeated with data baselined to a 20 s resting period before the start of each block (Fig. S3.1). These analyses showed the same results as presented here, and confirmed that the increase in beta modulation depth was exclusively due to a higher amplitude synchronisation phase.

The behavioural relevance of the increased modulation depth was underscored by a significant correlation between beta modulation depth in the contralateral hemisphere and reaction time (across groups), in both the non-rhythmic ($r = –0.46$, $P = 0.011$) and rhythmic condition ($r = –0.50$, $P = 0.005$) (Fig. S3.2).

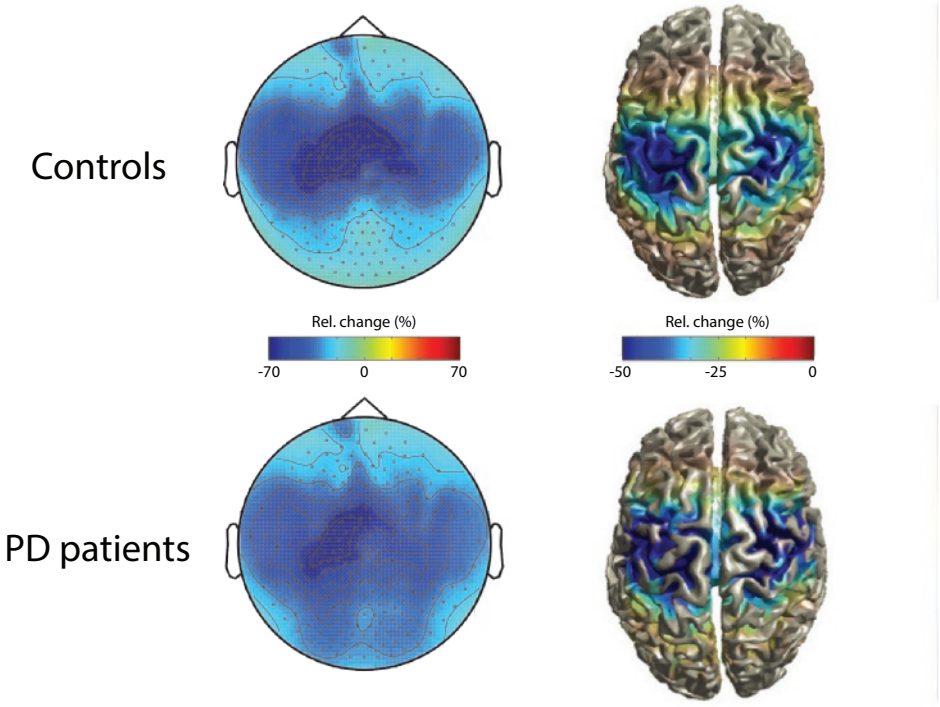

Figure 3.4 Spatial distribution of the beta power modulation (in % change), measured from maximal post-stimulus ERD to maximal ERS, at the sensor level (left panel) and projected onto an MRI-derived cortical surface (right panel). The topographies are averaged over both conditions and response hands (by first mirroring the topographies of the left hand condition over the anterior–posterior axis and then averaging over the right and left hand conditions), but separately for both groups (scaling of the PD group is increased by 10% for illustrative purposes). Thus, the left hemisphere sensors are contralateral, and the right hemisphere sensors ipsilateral to the side of movement.

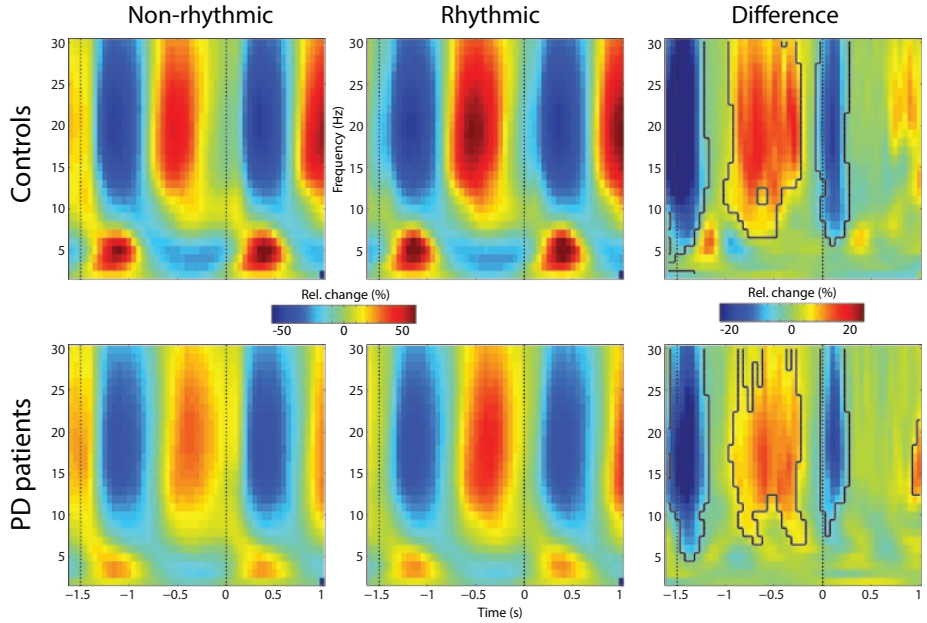

Figure 3.5 Time-frequency representations of the changes in spectral power in the contralateral sensorimotor area ROI (see Fig. 3.6C) for controls and PD patients in both the non-rhythmic and rhythmic conditions. The vertical dotted lines indicate stimulus onset. The power difference (rhythmic minus non-rhythmic) between conditions is represented in the right-most column. Black solid lines surround time-frequency clusters that are significantly different ($P < 0.05$) between conditions, as tested by means of a cluster-based nonparametric permutation test. Note, there are two significant clusters of beta ERD, of which the first is due to averaging of trials with non-equal SOAs preceding the standard 1.5 s interval in the non-rhythmic condition. The second cluster of ERD represents a sensory gating effect.

Predictive beta modulation

Predictive beta modulation was calculated as the percentage of beta modulation that occurred before stimulus onset (beta power change from maximal pre-stimulus ERS to stimulus onset) compared to the total beta modulation depth (beta power change between maximal ERS and subsequent maximal ERD). By definition, this means that a stronger ERS will lead to an increase in predictive beta modulation (assuming the ERD remains the same), while a stronger ERD phase leads to a decrease in predictive modulation. Across groups, the predictive beta modulation was higher in the rhythmic than non-rhythmic condition ($F(1,28) = 28.7$, $P < 0.0001$), which agrees with the higher amplitude ERS phase in the rhythmic condition. The predictive beta modulation was higher in the contralateral than ipsilateral hemisphere ($F(1,28) = 52.6$, $P < 0.0001$) and significantly lower in PD patients than in healthy controls ($F(1,28) = 4.9$, $P = 0.035$). There were no interactions involving the factors Group, Rhythmicity or Hemisphere.

There was a significant correlation (across groups) between predictive beta modulation in the hemisphere contralateral to the upcoming response hand and reaction time, in both the non-rhythmic ($r = –0.55$, $P = 0.002$) and rhythmic condition ($r = –0.72$, $P < 0.001$) (Fig. S3.2). The correlation between the between-conditions difference of both the predictive modulation and reaction time was also significant ($r = 0.46$, $P = 0.01$), meaning that the speeding of reaction time correlates with the increase in predictive beta modulation. Since we found a correlation between

reaction time and both the contralateral modulation depth and predictive beta modulation, we used partial correlations to find out which of the two best explained reaction time. There was a significant partial correlation between predictive beta modulation and reaction time, regressing out modulation depth, in both conditions (non-rhythmic: r = –0.48, P = 0.009; rhythmic: r = –0.66, P < 0.001). Partial correlations between modulation depth and reaction time, regressing out predictive beta modulation, showed a trend towards significance in both conditions (non-rhythmic: r = –0.36, P = 0.057; rhythmic: r = –0.35, P = 0.06). These findings indicate that both modulation depth and predictive modulation of contralateral beta oscillatory power are related to reaction time, the latter more robustly.

Based on previous studies showing a coupling between delta and beta oscillatory activity in rhythmic tasks, we investigated the correlation between the strength

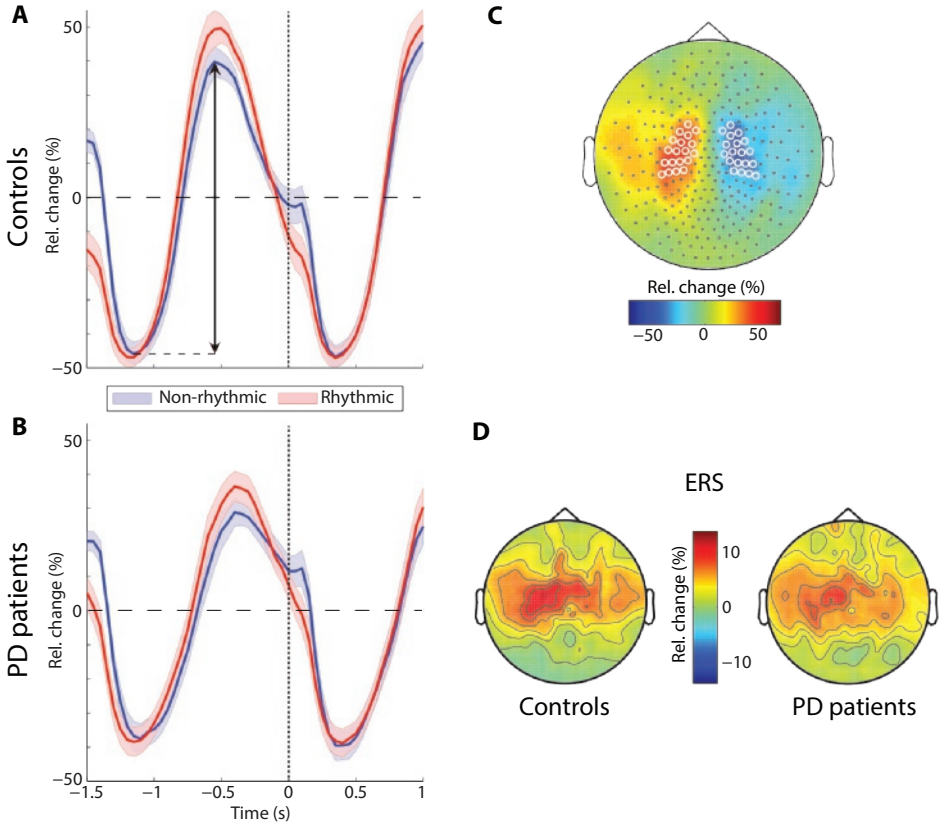

Figure 3.6 The group mean beta power changes over time, averaged across all beta frequencies (13–30 Hz) and all sensors overlying the ROI contralateral to the response hand (in C). Beta power traces are shown for controls (A) and PD patients (B) in the non-rhythmic (blue traces) and rhythmic (red traces) conditions. Beta modulation depth is equal to the difference between maximal pre-stimulus ERS and subsequent ERD trough (shown by the black arrow). Shaded areas around the mean beta power traces represent the SEM, and the vertical dotted line indicates stimulus onset. Topography of the difference in beta power between conditions is shown in (D), during a 200ms-window around the ERS peak (averaged across both hands, by first mirroring the topographies of the left hand condition over the anterior–posterior axis and then averaging over the right and left hand conditions).

of delta phase entrainment and the amount of predictive beta modulation. This correlation was significant in the rhythmic ($r = 0.38$, $P = 0.041$), but not in the non-rhythmic condition ($r = 0.09$, $P = 0.65$), supporting that phase-amplitude coupling of delta and beta oscillations may contribute to the behavioural advantage observed in the rhythmic condition.

Modulation of stimulus-evoked beta activity

In both groups, the beta power in the non-rhythmic condition briefly increased at a fixed latency of ~100 ms after stimulus onset, showing a small peak. In the rhythmic condition this peak reduced to a mere notch. The peak and notch correspond in time with a robust peak of beta synchronisation over posterior areas, at which location there was no amplitude difference between conditions. The short latency and temporal coincidence with posteriorly distributed beta synchronisation of high amplitude indicate that the central beta modulation concerns a modulation of stimulus-evoked beta activity. Importantly, the reduced beta power in the rhythmic condition reveals a gating of sensory input to sensorimotor areas due to further advanced movement preparation in this condition (Seki and Fetz, 2012). Within the sensorimotor cortex ROI, the size of the beta power difference between rhythmic and non-rhythmic conditions was identical between groups ($F(1,28) = 1.5$, $P = 0.23$). Analysis of this between-conditions effect across all sensors revealed a cluster of sensors in which beta power was significantly lower in the rhythmic compared to non-rhythmic condition for both controls ($P < 0.001$) and PD patients ($P < 0.001$). This effect displayed a focus over the contralateral sensorimotor cortex. The gating effect corroborates that the gain in beta modulation depth, the elevated beta-ERS, and the increased predictive beta suppression express increased preparatory activity due to a predictive mode of cue utilization.

3.4 Discussion

The main results of this study are, first, that PD patients benefit from a rhythmic compared to a non-rhythmic presentation of stimuli, both in terms of reaction time, entrainment of slow oscillations, and properties of beta oscillatory activity. Second, the entrainment of slow oscillations and the increase in modulation depth of beta oscillatory activity in PD patients, under a rhythmic stimulation regime, are identical to those in healthy control subjects. Third, the increase in modulation depth of beta oscillatory activity is, both in patients and controls, entirely due to an increased beta ERS phase that improves the predictive movement-related beta suppression, reflecting a predictive mode of cue utilization. Fourth, the beneficial effect of rhythmic stimulus presentation on reaction time, phase synchronisation of slow oscillations and predictive beta suppression, in both groups, are found against the backdrop of an overall significant group difference on these measures, with patients demonstrating slower reaction times, poorer phase synchronisation and smaller predictive beta suppression.

There is growing recognition of the role of temporal prediction in human behaviour (e.g. Calderone et al., 2014; Large and Jones, 1999; Schwartze and Kotz, 2013). One form of temporal prediction is based on environmental regularity, mediated by endogenous neural oscillations that align to regular external events (Schroeder

and Lakatos, 2009). This alignment occurs in such a way that timing of low and high excitability phases of neural oscillations are optimized to the processing of relevant events (Henry and Obleser, 2012; Lakatos et al., 2008). Entrainment of neural oscillations to the temporal structure of a task has demonstrated effects in a variety of behaviours and analyses of oscillatory entrainment are beginning to be applied to neurological and psychiatric disorders (Calderone et al., 2014; Lakatos et al., 2013b; Leong and Goswami, 2014; Praamstra and Pope, 2007; te Woerd et al., 2014). In PD such analyses have added relevance due to the wide application of rhythmic cueing in rehabilitation.

Investigations and reviews on cueing in PD frequently refer to compromised basal ganglia-cortical loops involving (pre-)SMA, resulting in impaired timing and impaired generation of internal cues for the sequencing of actions (Cunnington et al., 1995; Nombela et al., 2013; Rochester et al., 2007). External cues would improve motor function on the basis of increased activity of the lateral premotor cortex, probably supported by greater reliance on cerebellar-thalamocortical circuits, bypassing basal ganglia-thalamocortical loops (Benoit et al., 2014; Cunnington et al., 1995, 2001; Rochester et al., 2007; Samuel et al., 1997; Sen et al., 2010; Vercruysse et al., 2012; Yu et al., 2007). This view on cueing, assuming a shift in activation from medial to lateral premotor cortex and, subcortically, a shift from basal ganglia to cerebellum (Hughes et al., 2010), has also been criticized, however. It has been noted that there is no preferential involvement of the basal ganglia in internally generated movements (Ballanger et al., 2006; Turner and Anderson, 2005), and that functional specialization of medial and lateral premotor cortex for internally and externally cued movements is relative (Ballanger et al., 2006; Cunnington et al., 2002; Gowen and Miall, 2007; Jahanshahi et al., 1995). In a recent meta-analysis of imaging studies in PD, moreover, no evidence was found for a shift in activation from medial to lateral premotor areas (Herz et al., 2014a). Imaging studies comparing on and off states, furthermore, have shown that relative overactivation of lateral premotor cortex in PD is a feature of the off state only, eliminated by dopaminergic therapy which restores activity and connectivity of the SMA (Michely et al., 2015; Rowe et al., 2010). EEG studies using this approach revealed a similar pattern in restored oscillatory coupling of the SMA with prefrontal, premotor and motor cortex (Herz et al., 2014b, 2014c).

Recent work on rhythm perception has given an intriguing new perspective on this discussion. Grahn and Brett (2009) found impaired perception of beat-based rhythms in PD. Perception of such rhythms does indeed rely on activation of putaminal-premotor circuits with both SMA and lateral premotor cortex (Geiser et al., 2012; Grahn and Rowe, 2009), with the putaminal activation specifically serving beat prediction (Grahn and Rowe, 2013). As pointed out in the introduction, this raises an important question with respect to rhythmic cueing: if PD patients are impaired in the perception of beat-based rhythms with strong temporal regularity, how can they benefit from rhythmic cueing (Chen et al., 2009; Nombela et al., 2013)? A closely linked question, not addressed before, is whether a benefit, if it is there, preserves the predictive nature of putamen-premotor involvement in rhythm processing or takes a different, more reactive form.

Based on the available evidence on movement-related beta activity, we

hypothesized that a behavioural benefit of rhythmic stimulus presentation should be accompanied by an increase of beta power modulation depth in PD. We were specifically interested in whether such an increase is due to a gain in synchronisation or a gain in desynchronisation (see Fig. 3.1). Previously, we have observed a preserved modulation depth in PD, but with a shift from predominantly predictive to more reactive modulation. That is, relative to control subjects patients demonstrated little beta desynchronisation before the reaction stimuli, but a much larger desynchronisation after the stimulus, possibly in compensation (Praamstra and Pope, 2007; te Woerd et al., 2014). In a direct comparison of rhythmic and non-rhythmic stimulus presentation, this puts key significance on the sign of a gain in modulation depth. An increase in the synchronisation phase, with concomitant increase of predictive beta modulation fits the predictive nature of basal ganglia involvement in rhythm processing (Grahn and Rowe, 2009, 2013), and would provide an argument for rhythmic cueing to facilitate impaired basal ganglia-cortical communication. A qualitatively different increase in the desynchronisation phase, by contrast, would be an argument for beneficial effects of rhythmic stimulation to be based on mechanisms that perhaps bypass the basal ganglia. That is, preparatory adjustments enabled by rhythmic stimulus presentation may involve motor preparation, but also the presetting of stimulus processing mechanisms (Müller-Gethmann et al., 2003; Requin et al., 1991; SanMiguel et al., 2013b). When the latter form of preparation predominates, an increase in beta modulation depth may be reactive only.

The effects of rhythmic stimulus presentation were unambiguous. The gain in modulation depth was of the same size in patients and controls. In addition, the gain was entirely due to stronger synchronisation in both groups, which resulted in a significantly increased predictive beta suppression. Both these features are in agreement with the predictive nature of basal ganglia involvement in rhythm processing. Importantly, the sensory gating effect, which was of equal amplitude in patients and controls, provides strong confirmation of a predictive mode of cue utilization. Finally, the topographic distribution of the beneficial effects of rhythmic stimulation was identical between groups. This combination of results strongly suggests that the neural mechanism by which rhythmic stimulation facilitates movement is the same for patients and control subjects.

Serendipitously, the selective modulation, by temporal regularity, of the ERS phase of the movement-related beta amplitude modulation closely resembles a recently described effect on beta-ERS of movement errors in a visuomotor adaptation task (Tan et al., 2014a). The authors found a negative correlation between error size and amplitude of the beta-ERS phase, leading to the hypothesis that this beta-ERS effect serves the trial-to-trial modification of an internal model that guides future movement. In our experiment, the difference between actual and expected (mean or most frequent) interstimulus interval may also have acted as an error signal, influencing the beta-ERS modulation. The resemblance of the effects on beta-ERS is important for several reasons. Firstly, beta-ERS was hitherto understood as related to an idling state of the motor cortex or to sensory afferent processing (Cassim et al., 2001; Pfurtscheller et al., 1996). The proposed relation to updating of an internal model establishes a conceptual link between the amplitude of beta-ERS

and predictive beta suppression. That is, following successful performance post-movement beta-ERS will be higher than after an error, and act to preserve the set of motor commands that achieved the last response (Tan et al., 2014a). Conversely, reduced beta-ERS following an error provides the flexibility that is necessary for motor adjustments on the next trial (Brittain and Brown, 2014). Naturally, these different states yield different degrees of preparedness, expressed in predictive beta suppression. Secondly, Tan et al. (2014b) obtained similar effects in the subthalamic nucleus (STN) of (medicated) Parkinson patients, and complemented this observation with analyses of information exchange between STN and cortex. These analyses revealed an STN-driven coupling to the sensorimotor cortex after large errors which correlated with subsequent behavioural adjustment. This demonstrates that even in advanced PD the basal ganglia maintain a significant degree of involvement in adaptive behaviour and, most relevant here, are able to support the beta modulation we observe in this study. Note that we do not imply that the beta ERS effect reported by Tan et al. has the same underlying mechanism as the modulation we observe. The important resemblance is the association between ERS amplitude and preparation for a subsequent trial.

Returning to rhythm processing and entrainment in PD, there is a general view that basal ganglia and cerebellum represent different timing systems, beat-based and duration-based, respectively (Merchant et al., 2015; Teki et al., 2011). The distinction may explain why beat-based rhythms activate putamen-premotor circuits and rhythms without temporal regularity the cerebellum (Grahn and Rowe, 2013). However, a case has been made that the two systems do not operate independently, but in a coordinated fashion (Cope et al., 2014; Teki et al., 2012). In the unified timing model of these investigators, the basal ganglia are an obligatory component, required for duration-based as well as beat-based timing. Moreover, temporal prediction within a beat-based context is designated as a function crucially relying on the basal ganglia (Cope et al., 2014). Clearly, from the perspective of this model, our finding of a predictive mode of cue utilization in PD supports that the benefit of rhythmic stimulus presentation involves the basal ganglia, and calls the notion of a simple shift from basal ganglia-thalamocortical to cerebellar-thalamocortical pathways, as the basis for rhythmic cueing, into question.

Conclusion

There is a longstanding notion that PD patients do not optimally exploit advance information or easily engage in advance preparation, instead adopting a more reactive mode of responding. In line with this notion, the movement-related suppression of beta power in serial reaction tasks is predominantly reactive in PD patients and more prospective in healthy subjects (Praamstra and Pope, 2007; te Woerd et al., 2014). The present data show, however, that rhythmic vs. non-rhythmic stimulus presentation produces the same gain in beta modulation depth in patients and controls, exclusively due to a higher amplitude beta-ERS phase that increases the predictive, but not the reactive beta power suppression. Supported by recent work in areas of motor learning and timing, the results point to a facilitatory effect of rhythmic stimulation on basal ganglia-premotor cortex interaction, in patients and

controls alike. This outcome echoes the conclusion of Ballanger et al. (2006), stating that benefits of external cues reflect general properties of the motor system, rather than being due to recruitment of ancillary structures compensating for deficient basal ganglia-cortical projections. A limitation is that we used visual stimuli only, at a presentation rate slightly slower than optimal for inducing entrainment. However, with stimulus modality and frequency optimized to induce strong entrainment, the observed predictive mode of cue utilization is more likely to be strengthened than to be reversed.

3.5 Supplementary Figures

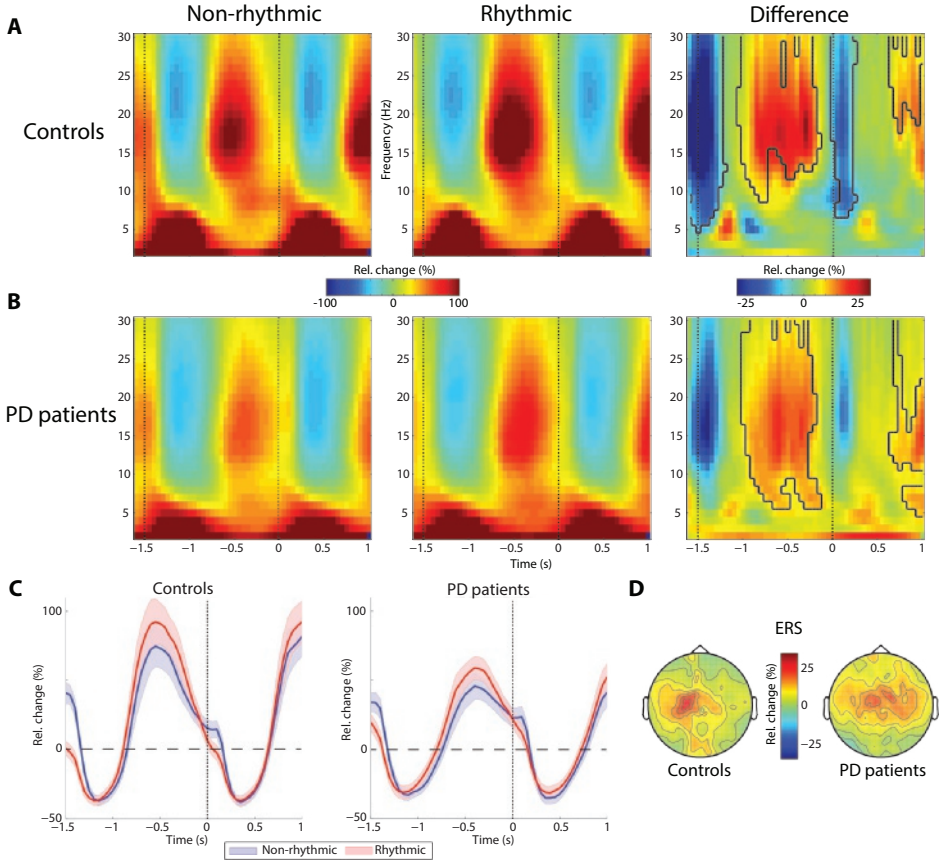

Figure S3.1 Time-frequency representations of the changes in spectral power (relative to a 20s baseline before the start of each block) over a region of interest overlying the contralateral sensorimotor area (see Figure 3.6C) for controls (A) and PD patients (B) in both the non-rhythmic and rhythmic conditions. The vertical oriented dotted lines show the time points of stimulus onset. The power difference (rhythmic minus non-rhythmic) between conditions is represented in the right column. Black solid lines surround time-frequency clusters that are significantly different ($P < 0.05$) between conditions. (C) The group mean beta power changes over time, averaged across all beta frequencies (13-30 Hz) and all sensors overlying the region of interest contralateral to the response hand. Beta power traces are shown for controls and PD patients in the non-rhythmic (blue traces) and rhythmic (red traces) conditions. Shaded areas around the mean beta power traces represent the SEM, and vertical dotted lines indicate stimulus onset. Topography of the difference in beta power between conditions is shown in (D), during a 200 ms-window around the maximal ERS phase (averaged across both hands, by first mirroring the topographies of the left hand condition over the anterior-posterior axis and then averaging over the right and left hand conditions).

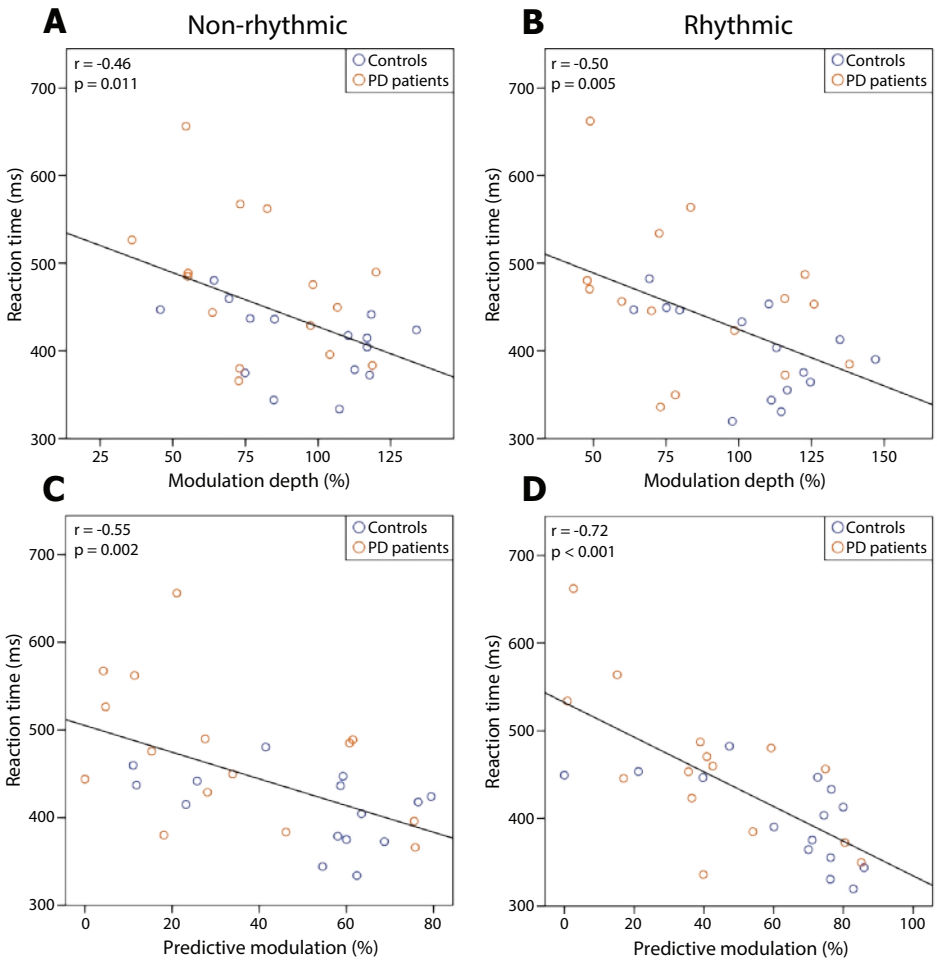

Figure S3.2 Correlations between reaction time and the beta modulation depth in the hemisphere contralateral to the response hand (A: non-rhythmic, B: rhythmic condition) and between reaction time and the contralateral predictive beta modulation (C: non-rhythmic, D: rhythmic condition). R-values in the top-left corners list the Pearson correlation coefficient of the two variables.

Impaired auditory-to-motor entrainment in Parkinson's disease

Adapted from
Impaired auditory-to-motor entrainment in Parkinson's disease.
te Woerd E.S., Oostenveld R., de Lange F.P., Praamstra P. (2017)
Journal of Neurophysiology: 117: 1853-1864

4

Abstract

Several electrophysiological studies suggest that PD patients have a reduced tendency to entrain to regular environmental patterns. Here we investigate whether this reduced entrainment concerns a generalized deficit or is confined to movement-related activity, leaving sensory entrainment intact. Magnetoencephalography (MEG) was recorded during a rhythmic auditory target detection task in 14 PD patients and 14 control subjects. Participants were instructed to press a button when hearing a target tone amidst an isochronous sequence of standard tones. The variable pitch of standard tones indicated the probability of the next tone to be a target. In addition, targets were occasionally omitted to evaluate entrainment uncontaminated by stimulus effects. Response times were not significantly different between groups and both groups benefited equally from the predictive value of standard tones. Analyses of oscillatory beta power over auditory cortices showed equal entrainment to the tones in both groups. By contrast, oscillatory beta power and event-related fields (ERFs) demonstrated a reduced engagement of motor cortical areas in PD patients, expressed in the modulation depth of beta power, in the response to omitted stimuli, and in an absent motor area P300 effect. Together, these results show equally strong entrainment of neural activity over sensory areas in controls and patients, but, in patients, a deficient translation of the adjustment to the task rhythm to motor circuits. We suggest that the reduced activation does not merely reflect altered resonance to rhythmic external events, but a compromised recruitment of an endogenous response reflecting internal rhythm generation.

4.1 Introduction

Sensory information from the environment can be rhythmic or non-rhythmic, and the brain is well-equipped to process both types of input. However, rhythmic stimuli have an advantage over non-rhythmic stimuli due to their temporal predictability, allowing the brain to entrain to the rhythm (Schroeder and Lakatos, 2009). Entrainment to external sensory input is suggested to align periods of high neuronal excitability with the onset of the behaviourally relevant stimuli (Lakatos et al., 2008). This alignment of the high excitation phase is suggested to allocate computational resources to a specific point in time, representing a neurophysiological basis for the Dynamic Attending Theory (Herrmann and Henry, 2014; Large and Jones, 1999). Several studies have shown beneficial effects of entrainment, in both the perceptual (Cravo et al., 2013; Mathewson et al., 2010) and motor domains (Morillon et al., 2016; Stefanics et al., 2010; van den Brink et al., 2014). Entrainment of oscillatory activity can occur in different frequency-bands, as studies have shown entrainment in the delta (Lakatos et al., 2008; Saleh et al., 2010), alpha (Spaak et al., 2014) and beta (Lakatos et al., 2013b; Miller et al., 2012) frequency ranges.

Studies on entrainment of delta and beta oscillations in Parkinson's disease (PD) have shown that patients show deficient entrainment compared to healthy controls (Praamstra and Pope, 2007; te Woerd et al., 2014, 2015). However, these studies only investigated entrainment over motor areas, leaving open the question whether deficient entrainment in these patients is a generalized deficit or a deficit confined to motor areas. This question has theoretical significance, but is also pertinent to the rehabilitation approach of rhythmic cueing. Cueing effects on motor activity are generally assumed to rely on entrainment. Entrainment of motor activity, and consequent improvement of motor performance, may be expected to be more effective when the relevant sensory modality has a spared rather than a compromised capacity for entrainment. This is underscored by recent reviews on cueing, which emphasize especially potent effects of rhythmic auditory stimulation, based on auditory-motor connectivity (Ashoori et al., 2015; Hove and Keller, 2015; Nombela et al., 2013). To date, however, it has not been assessed neurophysiologically whether rhythmic auditory stimulation (1) produces comparable auditory entrainment in PD patients and controls, and (2) whether between groups such auditory entrainment is equally potent in engaging motoric activity.

For several reasons, it is advantageous to address the question whether deficient entrainment in PD is generalized or specific to the motor system through the auditory modality. The auditory cortex is sufficiently far away from the motor cortex to spatially separate auditory and motor cortical rhythms. Equally important, the sensorimotor beta rhythm, with typically attenuated reactivity in PD (Devos et al., 2003; Heinrichs-Graham et al., 2013; Jenkinson and Brown, 2011; Labyt et al., 2003; Oswal et al., 2012), is also prevalent in the auditory cortex and is known to mediate auditory-motor interactions (Fujioka et al., 2012; Lakatos et al., 2013b). Finally, motor cortex beta reactivity during auditory target detection has proven to be sensitive to group differences in entrainability (Lakatos et al., 2013b). In light of this background, we used an auditory target detection task and recordings of oscillatory brain activity to test whether deficient entrainment in PD patients is a generalized deficit or restricted to the motor system.

4.2 Materials and methods

Table 4.1 Demographic and clinical characteristics of participating Parkinson patients. UPDRS motor score was determined directly after the experiment. Levodopa was always used with a dopadecarboxylase inhibitor. Pramipexole dose is given in terms of salt content.

Subject number	*Age (yrs) and gender*	*Years since diagnosis*	*Most affected side*	*UPDRS motor score*	*Dominant hand*	*Medication (daily dose)*
1	70, M	6	L	24	R	Pramipexole 1.5 mg Levodopa 450 mg Trihexyfenidyl 6 mg
2	57, M	8	R	31	R	Levodopa 500 mg
3	70, M	3	L	33	R	Levodopa 400 mg
4	67, M	7	L	31	R	Pramipexole 1.125 mg Levodopa 950 mg
5	67, M	2	L	23	R	Levodopa 450 mg
6	57, M	5	R	19	R	Levodopa 600 mg
7	62, M	17	R	22	R	Levodopa 500 mg Pramipexole 3.75 mg
8	56, F	5	L	18	R	Levodopa 300 mg
9	48, F	3	L	17	R	Pramipexole 0.75 mg Levodopa 300 mg
10	63, M	8	R	31	L	Levodopa 1000 mg Entacapone 1000 mg Amantadine 200 mg
11	61, M	10	L	44	R	Pramipexole 4.5 mg Levodopa 700 mg
12	47, M	3	R	34	R	Levodopa 500 mg Pramipexole 0.75 mg
13	58, M	16	L	34	R	Levodopa 450 mg Pramipexole 1.5 mg Amantadine 200 mg
14	69, M	15	L	30	R	Amantadine 200 mg Pramipexole 3.75 mg Levodopa 800 mg
Mean (±SD)	61 ± 8	8 ± 5		28 ± 8		

Subjects

A total of 15 PD patients and 15 healthy subjects participated in the experiment. One healthy subject performed the task with the non-dominant hand and one patient could not perform the task correctly; both were excluded from all further analyses. This left the final sample in the experiment with 14 PD patients (11 men; mean age ± SD, 61 ± 8 years; 1 left-handed) and 14 healthy age-matched subjects (9 men; aged 60 ± 5 years; 1 left-handed). Control subjects were without history of neurological or psychiatric disease. PD patients were of mild to moderate disease severity (see Table 4.1). All participants provided written consent and the study was approved by the local ethics committee (CMO Arnhem-Nijmegen). All patients were on dopaminergic medication, but the experimental investigation and UPDRS rating

were performed in the morning, after overnight withdrawal of medication (>12 h). The patient group had a mean score of 28 (±8) on the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS) in the OFF state (see Table 4.1).

Task and procedure

The experiment consisted of an auditory target detection task, based on a study of Stefanics et al. (2010). The auditory stimuli were presented at a comfortable hearing level, with a fixed stimulus onset asynchrony (SOA) of 1000 ms. Three cue tones of different frequencies (900, 1100 and 1300 Hz; 50 ms duration) predicted the probability (10%, 30%, 50%) of the next stimulus being the target tone (2000 Hz; 50 ms duration) (Figure 4.1A). The pitch of standard tones was chosen to be separated by 200 Hz and the target differed 700 Hz from the highest standard tone, which enabled subjects to detect the target tone easily. Participants were informed about the meaning of the standard tones and instructed to press the response button as swift as possible with the index finger of their dominant hand. Standard tones were presented with a ratio of 2:1:1 for the 10, 30 and 50% tones respectively, as this has two main advantages. First, adding more tones with 10% target probability leads to longer target-free periods, enabling the analysis of entrainment without movement-related activity. Second, by presenting the 30 and 50% tones equally often, we can rule out the possibility that any probability-related effects we find are simply due to a lower presentation rate of tones with higher predictive value. Additionally, at random time points a stimulus was omitted (with 10% probability of occurrence), enabling the investigation of preparatory effects without any confounding evoked activity due to stimulus presentation. In order to make an unbiased comparison between conditions (standards, targets and omissions) and probabilities, we randomly selected 100 stimuli of each type for analysis. All subjects first performed a practice block to learn the task, after which stimuli were presented in 10 series of 280 stimuli (~4.5 min) each, with a short break between each series.

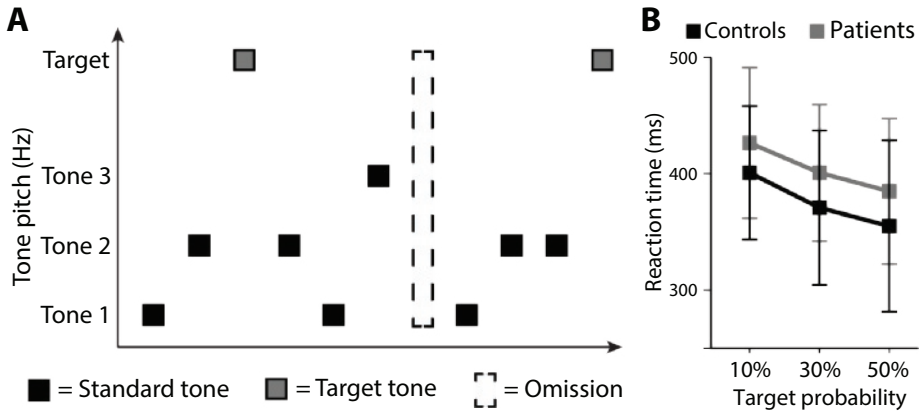

Figure 4.1 A) Schematic overview of the paradigm. B) Average response times to target tones for the different target probabilities and groups separately, error bars represent the standard error.

MEG recordings

Ongoing brain activity was recorded using a whole-head MEG system with 275 axial gradiometers (VSM/CTF Systems, Coquitlam, BC) in a magnetically shielded room. During the experiment, we continuously measured head position relative to the sensor array using localization coils that were placed at the nasion and in the left and right ear canals (Stolk et al., 2013). Vertical electro-oculogram (EOG) was recorded from the supra- and infraorbital ridges of the left eye, and horizontal EOG from the bilateral canthi. MEG and EOG data were sampled at 1200 Hz.

Behavioural analyses

Reaction time analyses were performed on the responses to the target tones, after excluding trials in which the response was too slow (>900 ms). Mean response times were determined for each target-probability (10%, 30% and 50%) separately. In addition, we calculated the overall percentage of detected target tones (percent correct) and calculated the false alarm rate for standard tones and tone omissions. As musical training could influence the experimental outcomes (Grahn and Rowe, 2009), all subjects filled out the subpart 'musical training' of the Goldsmiths Musical Sophistication Index (v1.0) (Müllensiefen et al., 2014). However, since musicality scores were not different between groups ($F1,26 < 1$) and none of the results were influenced by musical training, we will not further refer to this test.

MEG data analyses

MEG data were analyzed with MATLAB 2014a (Mathworks, Natick, MA) using the open-source FieldTrip toolbox (Oostenveld et al., 2011). For the main analyses, epochs of 5000 ms (3000 ms pre-stimulus and 2000 ms post-stimulus) were extracted from the continuous data separately for all conditions (standards, targets and omissions), based on the preceding standard tone. After removal of trials containing muscle artifacts, slow drift, or SQUID (superconducting quantum interference device) jumps, data were down-sampled to 400 Hz.

For the analyses of oscillatory entrainment, epochs of 7000 ms (4000 ms pre-stimulus and 3000 ms post-stimulus) were extracted from the continuous data using a sliding window approach. These epochs included all series of four consecutive standard and omitted tones (irrespective of probability), effectively using series of non-target tones to avoid any movement-related activity.

Independent component analysis was used to remove any remaining variance caused by eye blinks and heartbeat artifacts. As an extra check, the remaining data epochs were visually inspected and any epochs with artifacts were removed manually. The remaining stimulus-locked epochs were submitted to time-frequency and statistical analyses. All statistical analyses presented here were performed using SPSS version 19 (IBM Corp. Armonk, NY) and contained the factors Group (controls vs. PD patients) and Probability (10% vs. 30% vs. 50%) unless stated otherwise. MEG-data from left-handers was included in the signal average by mirroring the results over the anterior-posterior axis, and then averaging over all subjects.

Event-related fields

Before calculating the event-related fields (ERFs), all data were low-pass filtered using a 6th-order two-pass Butterworth filter with a cut-off frequency of 30 Hz. ERFs were baseline corrected by subtracting the mean signal amplitude in the 1100 to 900 ms pre-stimulus interval. A planar gradient transform was subsequently calculated (Bastiaansen and Knösche, 2000), which simplifies the interpretation of the sensor-level data by placing the maximal signal above the source.

Time-frequency analyses

Frequency decomposition was performed on the horizontal and vertical synthetic planar gradients of each channel, after which these were combined to obtain the oscillatory power at all channel positions. For all channels, time-frequency representations (TFRs) were calculated using a Fourier transform, applied to short sliding time windows across the entire length of the epochs, with a step-size of 10 ms. Before the Fourier transform, one or more tapers were multiplied to each time window and the resulting power estimates were averaged across tapers. The mean planar gradient power was estimated for all trials (within a condition and the three probabilities) in the frequency range 1-30 Hz (1 Hz frequency resolution) using a single Hanning taper and an adaptive time window of four cycles for each frequency. For the main analyses, the percentage change in oscillatory power was defined as the relative change with respect to the mean power in the 1100 to 900 ms pre-stimulus time window.

In the analyses of oscillatory entrainment, the power was defined as the relative change with respect to the mean power of the epoch (2000 ms pre-stimulus to 2000 ms post-stimulus). After this baseline-correction, beta power traces were calculated by averaging over the entire beta-band (13-30 Hz) for all time points and sensors separately. The beta traces were high-pass filtered using a 6th-order two-pass Butterworth filter with a cut-off frequency of 0.05 Hz in order to avoid drifts in these relatively long segments. To determine the strength of entrainment (defined as how strongly beta power modulates over time with the rhythm), we took the absolute of the beta power trace and calculated the area under the curve for the entire epoch (2000 ms pre-stimulus to 2000 ms post-stimulus).

Source analyses

Sources of event-related fields on the axial sensor data were identified using the minimum-norm estimate (MNE), as this approach is favoured for analyzing evoked responses. It estimates the amplitude of all modelled source locations on the cortical surface simultaneously and recovers a source distribution with minimum overall energy that produces data consistent with the measurement (Ou et al., 2008), as implemented in Fieldtrip (Oostenveld et al., 2011) according to the method of Dale et al. (2000). A realistic single-shell head model (Nolte, 2003) was created for each individual using the brain surface extracted from their individual segmented MRIs (7 out of 14 controls, 4 out of 14 patients) or from an MNI template-MRI (Holmes

et al., 1998). The source model was based on a template cortical sheet with 8196 vertices, which was spatially transformed from MNI space to the individual head coordinates on the basis of the transformation between MRI and MNI space. The subsequent source estimates of each individual were subsequently warped back to the template MRI in MNI coordinates. This warping procedure allows to directly average the source-reconstructed activity across subjects, restricted to a surface-based template.

For the analysis of delta phase entrainment, a virtual channel was created in the motor cortex contralateral to the response hand. The location of the motor cortex was estimated by using a frequency-domain beamforming approach on the axial sensor data. We contrasted the event-related desynchronization (ERD) (0.25-0.75 s post-target) with the event-related synchronization (ERS) (1-1.5 s post-target) activity for the center frequency of the beta band (22 Hz, resulting in 11 full cycles per time window). The same individual single shell head models as used in ERF source analysis were used, and the brain volume was discretized to a grid with an 8 mm resolution. A spatial filter was then constructed for each grid point using the cross-spectral density matrix and the forward solution for each grid point. The source power was calculated for the ERD and ERS windows, after which these were contrasted and the grid point with the maximal difference was identified as the location of interest in the contralateral motor cortex. We employed a time-domain beamformer to construct a spatial filter that passed the activity at the location of interest with unit-gain, while optimally suppressing all other contributions to the MEG data. The data were band-pass filtered between 0.05 and 3 Hz using a finite impulse response least squares filter. The instantaneous delta phase was calculated from the Hilbert transform of the band-pass filtered virtual-channel time series. To test if any phase preference was present for the instantaneous phases at stimulus onset, Rayleigh's test for non-uniformity of phase data was used (Fisher, 1993). The strength of phase preference (entrainment) was acquired by calculating the intertrial coherence (ITC) over all trials within each individual and separately for each target probability. The ITC ranges from 0 to 1, where 0 means no phase consistency and 1 is perfect phase consistency. Rayleigh's test and ITC calculations were performed in MATLAB using the circular statistics toolbox (Berens, 2009).

4.3 Results

Behavioural data

Subjects had to press a button as swiftly as possible when detecting a target tone within the isochronous stream of stimuli. For both groups, mean response time to targets decreased with increasing target probability (see Figure 4.1B), confirmed by a main effect of Probability ($F_{2,52} = 43.9$, $p < 0.0001$). Although PD patients appeared generally slower than healthy controls (Figure 4.1B), this effect was not supported by a significant difference between groups ($F_{1,26} = 1.5$, $p = 0.24$), nor was there an interaction between Group and Probability ($F_{2,52} < 1$). The percentage of correctly detected targets (controls: 99 ± 1%; PD patients: 98 ± 2%) was close

to ceiling level and did not differ between groups (F1,26 = 2.2, p = 0.15) nor did the false alarm rate (controls: 0.4 ± 0.3%; PD patients: 0.5 ± 0.3%) (F1,26 = 1.3, p = 0.27).

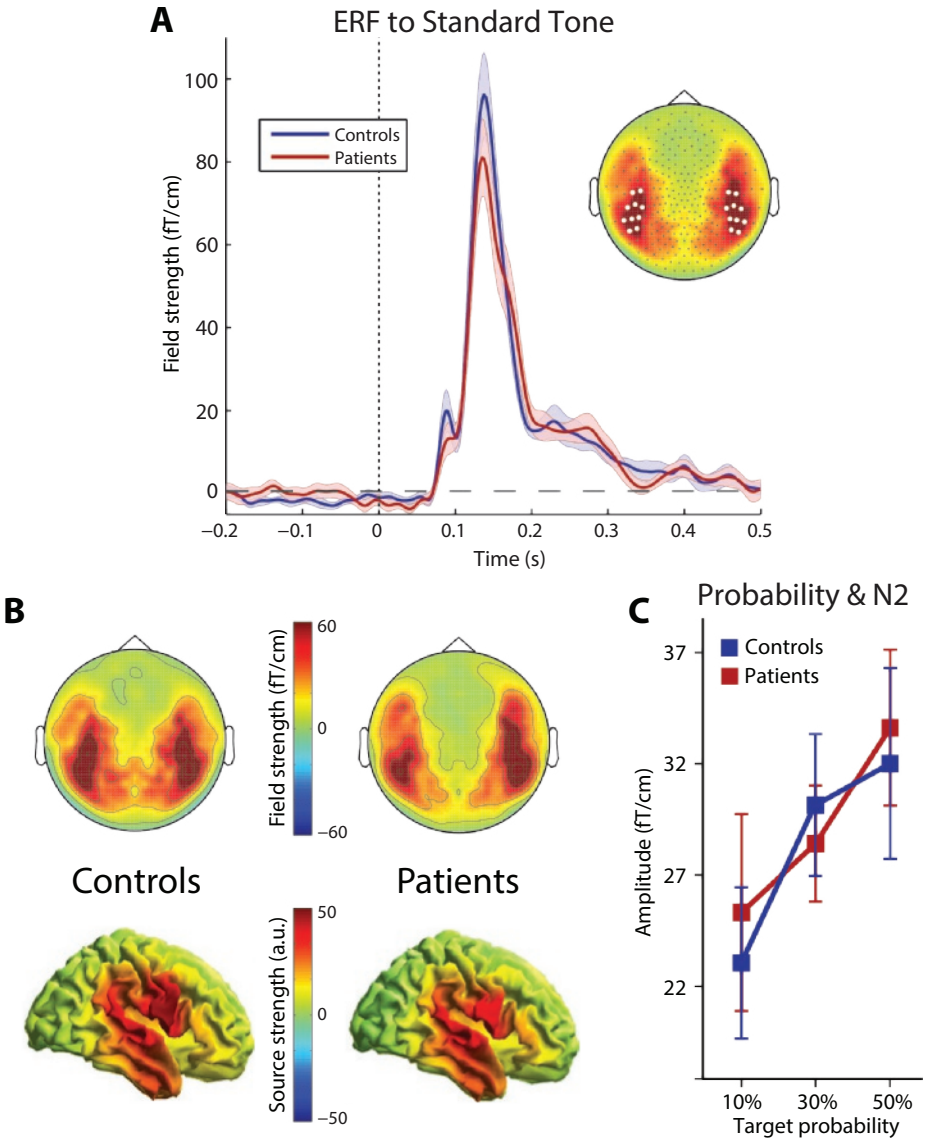

Figure 4.2 A) Average planar gradient evoked field over the auditory ROI (white sensors shown in inset) in response to a standard tone (averaged over the different target-probabilities), for controls (blue) and PD patients (red). Shaded area around the mean represents standard error. B) Top row: topographic distribution of the planar gradient evoked field elicited by a standard tone in a 50ms window centered around maximal ERF-value; bottom row: source reconstruction of the event-related field at maximal activation for both groups separately. C) Amplitude of the N2-component in the ERF, separately for all probabilities and groups, error bars represent the standard error.

Auditory activation does not differ between groups

To evaluate auditory processing, we defined an auditory ROI by averaging the evoked-field in response to standard and target tones (averaged over probabilities and groups) and selecting those maximally activated sensors per hemisphere that had a homologous sensor over the other hemisphere, yielding an ROI of 10 sensors (Figure 4.2A, inset). Standard tones produced a normal magnetic N1 response (Näätänen and Picton, 1987), reaching a maximal amplitude in both groups at 135 ms post-stimulus (Figure 4.2A), with the activity located over bilateral temporal cortices (see Figure 4.2B, top row). Statistical analysis by means of a cluster-based permutation test over the time interval of 1s pre-stimulus to 1s post-stimulus and all sensors in the auditory ROI indicated no differences in neural response to standard

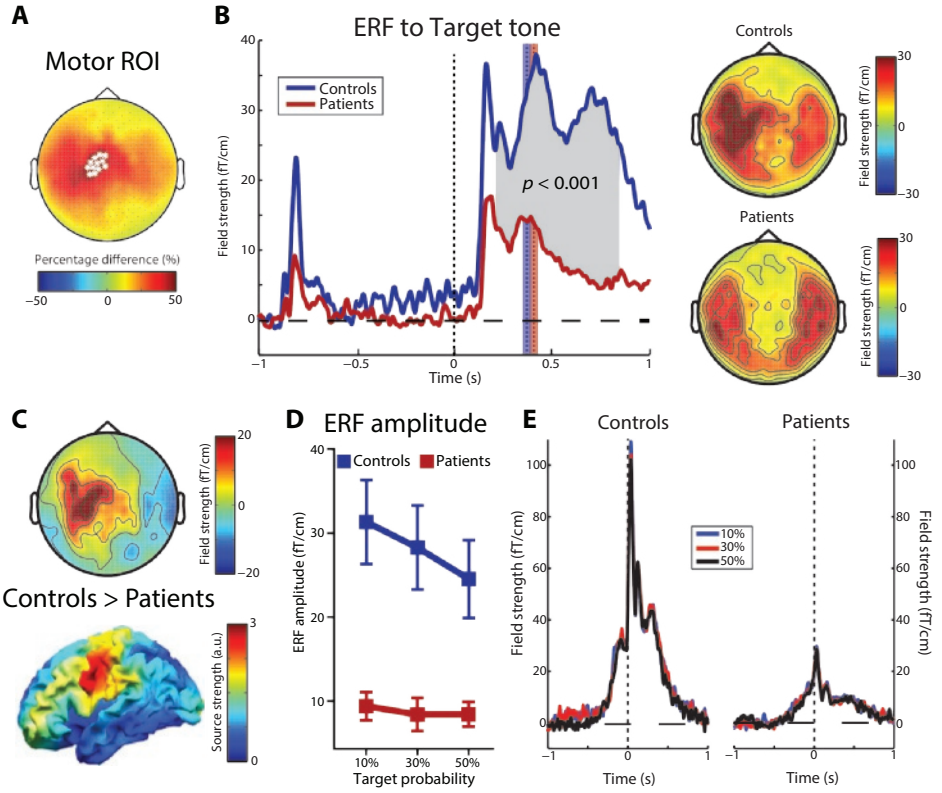

Figure 4.3 A) Topographical distribution of the modulation depth (difference between maximal ERD and ERS) of beta oscillatory power after a target tone, averaged over both groups and all probabilities. Sensors over which the modulation depth is strongest are shown in white and reflect the motor ROI. B) Average event-related fields over the motor ROI for the control (blue) and patient (red) groups, with the interval over which there was a significant difference colored in grey. Topography of the planar gradient event-related fields for both groups during the window of significance is shown on the right. The vertical oriented blue and red dashed lines indicate group mean response time for controls and patients respectively, with the shaded areas around this mean reflecting standard error. C) Topography of the difference in ERF amplitude between groups during the window of significance on sensor (top) and source level (bottom). D) Mean ERF amplitude over the motor ROI in (A) in the time window 200-950 ms post-target for the different target probabilities, separately for both groups and error bars represent standard error. E) Averaged response-locked ERF for the three probabilities and both groups.

tones between controls and PD patients ($p > 0.50$). Source reconstruction of the event-related field at the time point of maximal activation showed a bilateral source in superior temporal cortex and Heschl's gyrus for both groups (Figure 4.2B, bottom row).

To investigate whether both groups were equally proficient in extracting the predictive information from standard tones, we examined the amplitude of the auditory N2-component (defined as the maximum peak in the 200-300 ms post-stimulus time window). The N2-component is thought to reflect attentional allocation and stimulus classification or categorization (Näätänen et al., 2007; Sams et al., 1985; Tomé et al., 2015). Results of this analysis are shown in Figure 4.2C and show a significant effect of Probability ($F2,52 = 8.7$, $p = 0.001$), with the N2-amplitude being linearly related to the target probability signalled by the standard tone. There was no difference between groups ($F1,26 < 1$) and no interaction between Group and Probability ($F2,52 < 1$). These results thus indicate that both groups were equally well able to attend to the tones and classify their importance with respect to their predictive value. Note that it cannot entirely be excluded that the physical characteristics of the cue tones, which differed in pitch (900, 1100, 1300 Hz), may have influenced the N2 amplitude, although this is more likely for earlier components than for the N2.

Task and procedure

The experiment consisted of an auditory target detection task, based on a study of Stefanics et al. (2010). The auditory stimuli were presented at a comfortable hearing level, with a fixed stimulus onset asynchrony (SOA) of 1000 ms. Three cue tones of different frequencies (900, 1100 and 1300 Hz; 50 ms duration) predicted the probability (10%, 30%, 50%) of the next stimulus being the target tone (2000 Hz; 50 ms duration) (Figure 4.1A). The pitch of standard tones was chosen to be separated by 200 Hz and the target differed 700 Hz from the highest standard tone, which enabled subjects to detect the target tone easily. Participants were informed about the meaning of the standard tones and instructed to press the response button as swift as possible with the index finger of their dominant hand. Standard tones were presented with a ratio of 2:1:1 for the 10, 30 and 50% tones respectively, as this has two main advantages. First, adding more tones with 10% target probability leads to longer target-free periods, enabling the analysis of entrainment without movement-related activity. Second, by presenting the 30 and 50% tones equally often, we can rule out the possibility that any probability-related effects we find are simply due to a lower presentation rate of tones with higher predictive value. Additionally, at random time points a stimulus was omitted (with 10% probability of occurrence), enabling the investigation of preparatory effects without any confounding evoked activity due to stimulus presentation. In order to make an unbiased comparison between conditions (standards, targets and omissions) and probabilities, we randomly selected 100 stimuli of each type for analysis. All subjects first performed a practice block to learn the task, after which stimuli were presented in 10 series of 280 stimuli (~4.5 min) each, with a short break between each series.

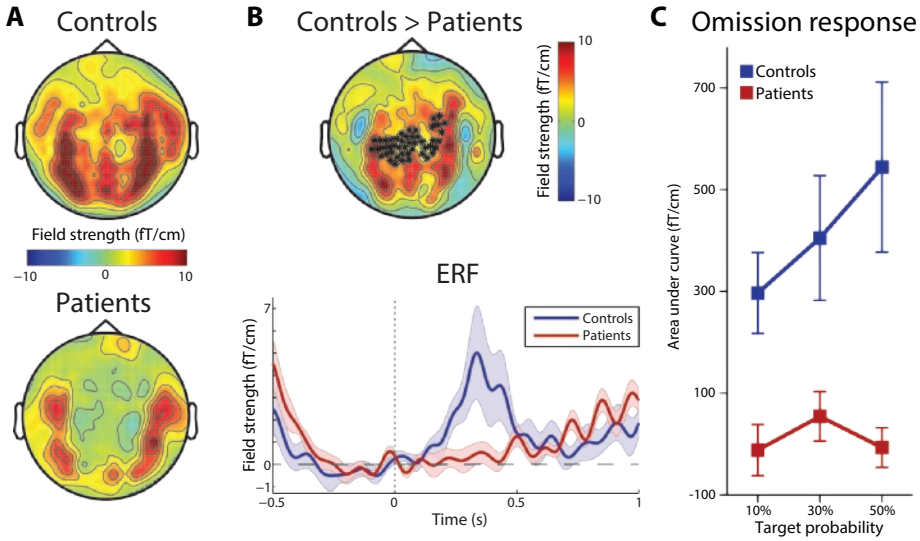

Figure 4.4 A) Topographical distribution of the omission response in controls (top) and patients (bottom), during a 200 ms time window centered on maximal omission response. B) The difference in evoked field between groups (top) with sensors in black being significantly different ($p < 0.05$) between groups. The average ERF over these sensors shows a clear omission response in controls but not in patients (bottom; shaded area around the traces reflects the standard error). C) Size of the omission response (defined as the area under the curve during a 200ms window around maximal omission response) for the different target probabilities and groups separately with the error bars representing standard error.

Tone omissions show deficient engagement of central areas in PD

Omitted tones elicited neural activity over the auditory ROIs in both groups, with a peak at 335 ms post-stimulus in the ERF averaged over both groups and all probabilities. To gain more insight in the omission response, we plotted the topographical distribution of this effect in a 200 ms time window centered on the peak. This analysis showed strong lateral-parietal activation in both controls (Figure 4.4A, top) and patients (Figure 4.4A, bottom). The topographical distribution plots suggest stronger activation of the central-parietal areas in controls than in patients, which is supported by a cluster-based permutation test showing a significant difference between groups ($p < 0.05$) with a cluster overlying these areas (Figure 4.4B, top). The ERFs over this cluster of sensors are shown in Figure 4.4B (bottom, averaged over all probabilities), showing a clear omission response in controls but not in patients. A more detailed analysis of the peak ERF-amplitude in the 200-400 ms post-omission time window, confirmed a higher amplitude in controls as shown by a main effect of Group ($F1,26 = 4.9$, $p = 0.035$). There was a trend towards a main effect of Probability on ERF amplitude ($F2,52 = 3.0$, $p = 0.06$), with a higher amplitude omission-response after higher target probability. There were no significant interactions involving Group or Probability.

Auditory versus motor entrainment

The previous results were all suggestive of intact auditory, but possibly deficient motor activation in PD. In order to investigate this more directly, we calculated the spectral power changes over both the auditory and motor ROIs (Figure 4.5A), and further examined auditory and motor function in a single analysis of beta power entrainment. Since oscillatory activity in the beta-band (13-30 Hz) has an important role in both the motor and auditory cortex, and is known to mediate auditory-motor interactions (Fujioka et al., 2012; Lakatos et al., 2013b), we analyzed entrainment of oscillatory beta activity by calculating beta power traces over the auditory (Figure 4.2A) and motor (Figure 4.3A) regions for both groups separately. These traces were averaged over segments of four consecutive non-targets, to avoid any movement-related activity, but included besides standard tones occasional omitted tones. The resulting beta power traces are shown in Figure 4.5B. The time course of beta power changes is such that there is a reduction in power starting well before stimulus occurrence, supporting that the changes reflect a predictive adjustment of cortical excitability (Lakatos et al., 2013b), and thus represent a form of entrainment rather than an evoked change. An evoked effect is nonetheless clearly present in the beta power trace for the auditory ROI at a short latency following the stimulus.

The beta power traces over the auditory ROI are virtually identical for both groups, unlike the power traces over the motor ROI, where patients show a pronounced reduction in the magnitude of power change for each single ERD and ERS phase. Defining entrainment of beta power in terms of the modulation depth, the figure shows normal entrainment over the auditory ROI but deficient entrainment in patients over the motor ROI. To quantify this effect, we calculated the absolute area under the curve for both groups and ROIs (Figure 4.5C), with more area under the curve indicating a stronger entrainment. This analysis showed a significant interaction between Group and ROI ($F_{1,26} = 10.8$, $p = 0.003$), resulting from stronger entrainment over the motor ROI in controls compared to patients, but no difference between groups over the auditory ROI. These results are confirmed by an analysis over all sensors, showing clear entrainment of beta activity over auditory cortices for both groups (Figure 4.5D), but reduced entrainment in patients specifically located over the (contralateral) motor cortex (Figure 4.5E). The results furthermore show that the entrainment of beta oscillatory power is only found over the auditory and motor areas, confirming the importance of these oscillations in auditory-motor interactions (Fujioka et al. 2012), and suggesting that the automatic entrainment of motor areas to the task rhythm, as seen in healthy controls, is impaired in PD.

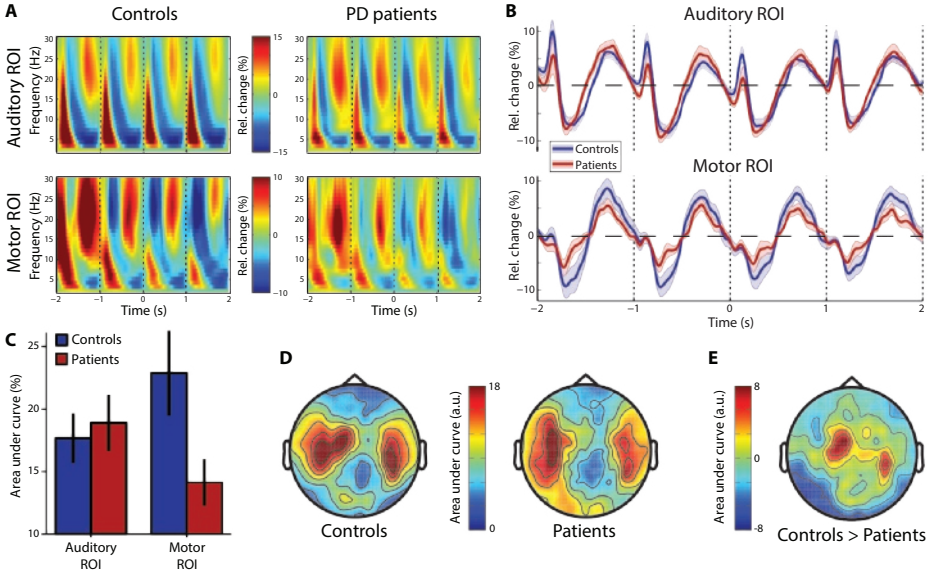

Figure 4.5 A) Time-frequency representations of relative power changes to baseline for both controls and PD patients separately. Top-row shows spectral power changes over the auditory ROI (see Figure 4.2A) and bottom-row for the motor ROI (see Figure 4.3A). (B) Beta power traces in time over the auditory ROI in the upper row, and for the motor ROI in the bottom row. These traces are averaged over four consecutive non-targets (standard and omitted tones), leaving out any confounding movement-related activity. The shaded areas around the mean represent the standard error. (B) Overview of the area under the curve in A for both groups and ROIs, showing a difference between groups over the motor but not the auditory ROI. Error bars represent the standard error. (C) Topography of beta power entrainment in both controls (left) and patients (right), with the difference between groups shown in (D).

Strength of motor activation varies with predictive value

The predictive value of each tone is used to set the motor cortex to an appropriate state of readiness as asked for by the tone. An index of the state of readiness of the motor cortex is beta ERD (Kilavik et al., 2013; Oswal et al., 2012). We investigated whether the predictive value of standard tones is reflected in the amount of beta ERD induced over the motor cortex. Therefore, we calculated beta power traces over time for all sensors within the motor ROI for tone omissions (Figure 4.6A). There was a significant main effect of Probability on the amount of beta ERD ($F_{2,52} = 17.8$, $p < 0.0001$), explained by more ERD with higher target probability of the standard tone preceding the omission (Figure 4.6B, left panel). There was a non-significant trend towards a difference between groups ($F_{1,26} = 3.9$, $p = 0.058$), with cue tones inducing more beta ERD in controls than in patients. The interaction between Group and Probability also showed a trend towards significance ($F_{2,52} = 3.0$, $p = 0.059$), suggesting a graded activation of the motor system dependent on the likelihood of a target (signalled by the predictive value) in controls, but not in patients.

To test whether the ERD due to the standard tones indeed prepares the motor system for an upcoming target, we investigated beta power after stimulus omissions. In omission trials the prepared motor response should be inhibited/withdrawn and the strength of inhibition should match the strength of preparation. Additionally, the

omission condition gives the opportunity to study anticipatory processes without any confounding evoked activity due to stimulus presentation. Hence, we evaluated whether the amount of beta ERS (a marker of movement suppression; Androulidakis et al., 2007a) after an omission depended on the preceding standard tone. This analysis revealed a significant effect of Probability on post-omission beta ERS ($F2,52 = 10.6$, $p = 0.0001$), showing a stronger post-omission beta ERS with higher target probability (Figure 4.6B, right panel). There was also a significant difference between groups ($F1,26 = 4.6$, $p = 0.042$), indicating stronger beta ERS in controls than in PD patients, a finding that conforms to the earlier finding of reduced beta ERD in patients. There was no significant interaction between Group and Probability ($F2,52 = 1.1$, $p = 0.33$).

To test the relation between beta ERD (response preparation) and ERS (response inhibition) more directly, we determined the correlation between these two variables. Over groups, there was a significant (positive) Pearson correlation between the amount of beta ERD induced by a standard tone and the amount of beta ERS after an omitted tone ($r = 0.51$, $p < 0.0001$; Figure 4.6C). This correlation was also significant for the control ($r = 0.57$, $p < 0.0001$), and patient ($r = 0.34$, $p = 0.03$) groups separately, albeit considerably lower for patients. These effects on beta power during stimulus omissions complement the earlier finding of impaired motor entrainment in PD patients. Despite the reduced entrainment, patients are still able to modulate the strength of motor preparation according to the predictive value of standard tones, where a tone with high predictive value leads to stronger motor activation (larger beta ERD, followed by subsequent larger beta ERS).

Besides beta oscillations, also slow delta oscillations play a functional role in anticipatory mechanisms by means of increased phase synchronization with stronger target probability (Stefanics et al., 2010). We evaluated this in our data with an analysis of delta phase synchronization performed on the signal in a virtual channel, located in the motor cortex contralateral to the response hand of each individual. Delta phase analyses were only performed on trials in which the stimulus was omitted, as these trials are not contaminated by stimulus evoked or motor activity. In general, there was a significant entrainment of delta oscillations (Rayleigh's test for non-uniformity with $p < 0.05$) to the task rhythm (Figure 4.6D), with no difference between groups ($F1,26 < 1$). This was confirmed by additionally testing the resultant vector length of the phase distributions of both groups against a reference distribution of vector lengths originating from 10.000 randomly generated uniform phase distributions, confirming significant phase preference (non-uniformity) for both controls ($p = 0.01$) and patients ($p = 0.03$). When investigating the strength of entrainment for the different target probabilities, there was a significant effect of target probability on delta ITC ($F2,52 = 7.6$, $p = 0.001$), showing that higher target probability leads to stronger phase synchronization of delta oscillations (Figure 4.6E). The interaction between Group and Probability was not significant ($F2,52 < 1$).

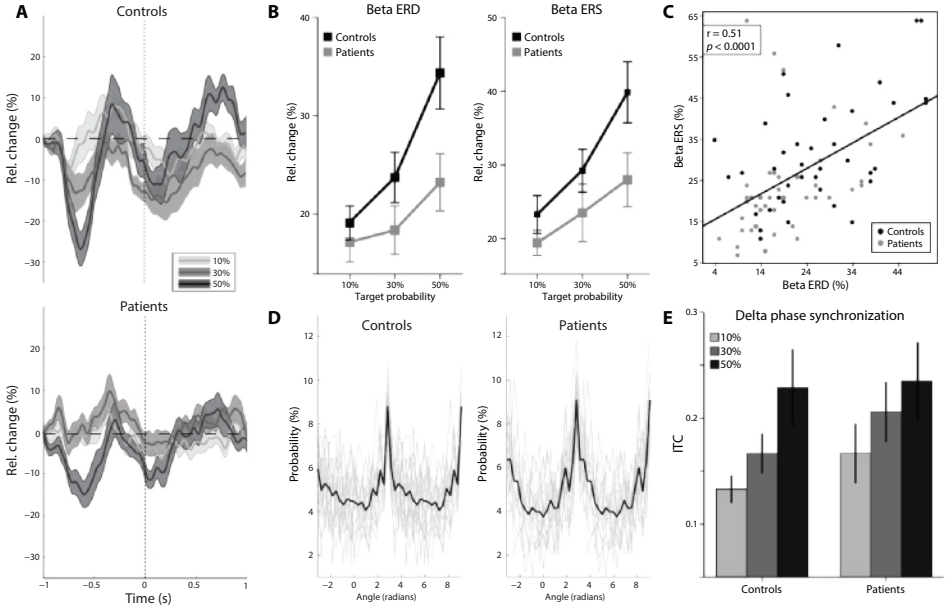

Figure 4.6 (A) Beta power in time over the motor ROI shown in Figure 4.3A, for the tone omissions (at t = 0s), separately for all target probabilities and both groups. The shaded areas around the traces represent the standard error. (B) Left: Size of beta ERD due to the tone preceding the tone omission, for the different target probabilities and groups separately; Right: Size of the beta ERS following the omitted tone, sorted by the tone preceding the omission. Error bars represent the standard error. (C) Correlation between the amount of beta ERD preceding the omission and the size of beta ERS after a tone omission. (D) Distribution of instantaneous delta phase in the motor cortex contralateral to the response hand at onset of omitted stimulus, aligned at the preferred phase for all individuals and averaged over the different target probabilities. (E) Values of delta phase intertrial coherence (ITC) in contralateral motor cortex during tone omissions, separately for the different target probabilities and groups, with the error bars reflecting standard error.

4.4 Discussion

This study investigated automatic entrainment to an isochronous stimulus stream, combined with a manipulation of expectancy based on predictive information conveyed by the pitch of individual stimuli in the stimulus stream. Stefanics et al. (2010) demonstrated that, in such a paradigm, exploitation of predictive information modulates delta activity synchronized to the regular stimulus stream, expressed in stronger phase synchronization with higher levels of expectancy. Our results show that Parkinson patients are just as proficient as healthy controls in extracting the predictive information, demonstrating similar reaction time benefits and similar effects on delta phase concentration. By contrast, automatic entrainment to the task rhythm was impaired in patients, as expressed in a reduced beta modulation depth over the motor cortex, in the presence of normal entrainment of auditory cortex beta activity.

Deficient entrainment in PD is confined to motor areas

Participants could make use of the temporal predictability of targets induced by the isochronous stream of stimuli. This temporal predictability allows subjects to deploy their attention to a particular moment in time, speeding up processing in sensory and motor domains (Correa et al., 2005; Griffin et al., 2002; Nobre et al., 2007). Studies investigating the neural mechanisms underlying this effect, have suggested an important role for oscillatory activity, especially when stimuli are presented in a rhythmic fashion (for review see Calderone et al., 2014). These studies have shown that rhythmic stimuli allow brain oscillations to entrain (phase-align) to the rhythm, thereby optimizing the processing of stimuli to which they synchronize (Cravo et al., 2013; Henry and Obleser, 2012; Lakatos et al., 2008). In addition to the entrainment induced by an isochronous stimulus presentation, the strength of target expectation was manipulated, following Stefanics et al. (2010), who found a positive correlation between delta phase synchronization and target probability. Our data replicate this finding and show that both healthy controls and PD patients varied the strength of delta phase concentration with target expectancy. For the patient group, this result was somewhat unexpected, as our previous work showed reduced entrainment of slow delta oscillations in PD patients (te Woerd et al., 2014, 2015). The preserved delta phase concentration supports the point made by Stefanics et al. (2010) that delta phase entrainment is more than a mechanistic consequence of periodic stimulation, and thus can be modulated by expectation. PD patients adequately extracted the probability information from the cues and expectation-driven phase synchronization may have masked any group difference in more spontaneous bottom-up alignment of delta phase due to temporal regularity. While PD patients may not exploit advance information as efficiently as controls, they can exploit it if the advance information is more explicit (Cunnington et al., 1999; Praamstra et al., 1996b), as it was in the present task.

PD patients' adequate use of explicit cue information may have masked their deficient use of the implicit cue of regular stimulus presentation, resulting in reaction times that were not significantly different from controls. In earlier studies (Praamstra and Pope, 2007; te Woerd et al., 2014), reduced entrainment in terms of oscillatory activity was also not expressed in reaction times, whereas a group difference in reaction time was found in te Woerd et al. (2015). A likely factor explaining the relative insensitivity of reaction time in comparison to robust group differences in task-related oscillatory activity is the simple button-press motor response. It is known that in tasks involving a movement, movement time is more sensitive to group differences than reaction time (Harrison et al., 1995). Moreover, it has been shown by means of transcranial alternating current stimulation (tACS) that increased synchronization of beta oscillations, as typically seen in PD, affects movement duration rather than reaction time (Pogosyan et al., 2009).

The beta rhythm has always been viewed as a rhythm particularly important in the motor system, but recent studies have shown an equally important role of beta oscillations in other cortical areas and functional domains. Most important in the current context are studies showing a role for beta oscillations in beat perception (Iversen et al., 2009), temporal prediction and attention in auditory cortex (Todorovic

et al., 2015), coupling between auditory and motor areas (Fujioka et al., 2012; Lakatos et al., 2013b) and timing of internally driven behaviour (Bartolo et al., 2014; Kononowicz and van Rijn, 2015). The finding of reduced entrainment of beta oscillatory power over motor areas indicates a deficit in translating the sensory entrainment to motor circuits. This is most likely due to disease-related changes within the motor system, rather than due to compromised auditory-motor pathways. Motor circuits have been attributed a role in internal rhythm generation (Bartolo et al., 2014; Teki, 2014), a process crucially relying on interactions between the basal ganglia and premotor areas (Grahn and Rowe, 2009, 2013). Several studies investigating oscillatory signatures of temporal prediction (or internal rhythm generation) have suggested that these predictions are sustained by beta-band oscillations in basal ganglia-cortical circuits (Arnal, 2012; Bartolo et al., 2014; Merchant and Yarrow, 2016).

The results of this study, with normal entrainment of sensory areas, but impaired engagement of motor areas in PD, fits the above framework. It has to be acknowledged, though, that this framework incorporates a dynamic rather than unidirectional interaction between basal ganglia motor circuits and sensory structures (Merchant and Yarrow, 2016; Morillon et al., 2016). Hence, it is not inconceivable that dysfunction in motor circuits may lead to altered entrainment of the auditory cortex and altered auditory-sensory prediction as well (Morillon et al., 2014). As a rule, however, Parkinson patients do not report difficulties in sensing a regular beat or less enjoyment of music (Nombela et al., 2013; Skodda et al., 2010). By contrast, they are impaired on beat-based rhythm discrimination tasks, dependent as they are on rehearsal and internal generation of a rhythm (Cameron et al., 2016; Grahn and Brett, 2009). Moreover, in synchronization-continuation tasks, PD patients perform equal to control subjects during the synchronization phase, but perform significantly worse during the continuation phase where internal rhythm generation is required (Elsinger et al., 2003; Tolleson et al., 2015).

Interestingly, the results bear a similarity to markedly attenuated rhythmic modulation of beta amplitude in schizophrenia patients, likewise obtained in a target detection task (Lakatos et al., 2013b). The similarity may be explained by the schizophrenia patients being treated with dopamine receptor blocking anti-psychotic drugs, yielding effects resembling dopamine deficiency in PD. Of note, the authors interpreted the attenuated modulation of beta power as an effect arising in auditory, rather than motor cortex, in spite of a strongly lateralized scalp distribution. Indeed, our robust separation of auditory and motor cortex beta activity depends on the use of MEG and would have been difficult with EEG.

Note that time-frequency analyses in this study were confined to the beta frequency band, as an important rhythm in both auditory and motor function, and the delta frequency band corresponding to the stimulation frequency. Other frequency bands might also be engaged, which could be worth investigating in future studies.

Effects of target probability over auditory and motor areas

Participants could use the predictive value of standard tones to anticipate targets, and response times show that both groups were able to speed up their responses with target probability, a result aligning with earlier work (Stefanics et al., 2010). Analyses of neural activity showed clear effects of target probability. First, we found that the N2-amplitude (reflecting attentional allocation and stimulus classification; Mueller et al., 2008; Näätänen et al., 2007; Sams et al., 1985; Tomé et al., 2015) in ERFs over auditory areas showed a linear relation with the predictive value of that tone. The absence of a difference in N2-amplitude between groups and the absence of an interaction between Group and Probability rule out that reduced entrainment of motor areas in patients is due to a failure to attend to or discriminate the cues. Rather, adequate exploitation of cue information may have helped patients to overcome the disadvantage of their motor cortex' state of response readiness not tracking the stimulus stream as well as controls.

Second, healthy control subjects, but not PD patients, demonstrated a decreasing ERF-amplitude with increasing target probability over the motor cortex, in addition to a markedly higher amplitude. This probability effect on ERF-amplitude may be related to the P300 even though this component is not prominently expressed in MEG recordings (e.g. Wacongne et al., 2011). A P300 effect is to be expected following infrequent targets, and its amplitude is plausibly attenuated when a preceding cue more strongly predicts its occurrence (Polich, 2012). Moreover, the P300 has a significant contribution from the motor cortex (Bledowski et al., 2004), has been proposed to serve a role in linking stimuli to responses (Verlegen et al., 2005; Verleger et al., 2014), and is frequently reported to have a reduced amplitude in PD (e.g. Pulvermüller et al., 1996). If the post-target ERF differences between patients and controls are indeed due to P300-related processing differences, than patients may be more reliant on the relative salience of the targets than controls. Recall in this context that the N2-amplitude modulation indicated that patients adequately processed the probability information of the cues, and also demonstrated a normal modulation of response times by this information. However this information had less of an impact on the preparatory state of the motor cortex as expressed in beta-ERD.

Third, the neural response to omitted tones was largest when preceded by the tone signaling target occurrence with highest probability. This behaviour is in line with the omission-response reflecting a form of a prediction error. Predictive coding models posit that unexpected events lead to more neural activity than expected events (Rao and Ballard, 1999), suggesting that the brain acts as a probabilistic inference machine continuously forming predictions about future input (Friston, 2010). Some authors have even suggested that the omission response reflects a "pure expectation" signal (SanMiguel et al., 2013b). In this condition the effect of target probability on signal amplitude is reversed compared to the tones, as now a strong prediction leads to a larger mismatch between expected and incoming signals and thus a larger neural response. This result agrees with previous work on auditory processing and tone omissions, arguing for predictive processing in audition (Bendixen et al., 2012; Todorovic and de Lange, 2012; Wacongne et al.,

2011) and showing that stronger predictions about an upcoming stimulus lead to larger omission responses when that stimulus is omitted (Jongsma et al., 2005; SanMiguel et al., 2013a; Todorovic et al., 2011). The fact that patients only showed an omission response over lateral parietal areas and not over central (motor) areas, like controls, supports the conclusion, from the analyses of beta activity, that the regular task structure fails to engage motor circuits in a predictive mode of function (Chennu et al., 2013; te Woerd et al., 2014; Wacongne et al., 2011).

Conclusion

The present results show that the engagement of cortical motor areas by attentive listening to a regular stimulus stream is considerably reduced in PD patients compared to healthy controls. This is expressed in the modulation depth of beta power, but also in the response to omitted stimuli and in an absent motor area P300 effect. The results fit a framework in which basal ganglia-cortical motor circuits are critical to predictive behaviour, mediated by hierarchically nested oscillatory synchronization (Morillon et al., 2015). Activity in the beta band may be especially important for establishing an internal model or sustain a rhythmic set (Bartolo et al., 2014; Merchant and Yarrow, 2016; Teki, 2014). Converging with this view, the ERS phase of rhythmic modulations in beta power was suggested to reflect trial-to-trial modification of an internal model guiding movement (Tan et al., 2014a, 2014b; te Woerd et al., 2015). If so, and if oscillatory activity in the beta band supports such a function, then the attenuated modulation depth of motor cortical beta activity, in our data, does not merely reflect altered resonance to rhythmic external events, but a compromised recruitment of an endogenous response, i.e., rhythmic set (cf. Bartolo et al., 2014). Ongoing work in which we instructed PD patients to selectively attend to one of two concurrently presented stimulus streams, supports this hypothesis.

Entrainment for attentional selection in Parkinson's disease

Adapted from
Entrainment for attentional selection in Parkinson's disease.
te Woerd E.S., Oostenveld R., de Lange F.P., Praamstra P. (2018)
Cortex: 99: 166-178.

5

Abstract

Neural entrainment plays a crucial role in perception and action, especially when stimuli possess a certain temporal regularity, and is also suggested to serve as a neural process to select and attend the relevant stream in situations where there are competing stimulus streams. Beneficial effects of entrainment have led to the suggestion that rhythmic stimuli can improve motor function in patients with Parkinson's disease (PD). Behavioural studies support this suggestion, but neurophysiological studies have shown reduced entrainment of motor areas in PD. However, oscillatory entrainment in PD has only been tested in paradigms with a single isochronous stimulus stream, whereas entrainment has an enhanced benefit in situations where one rhythmic stimulus stream has to be segregated from distractor stimuli. Therefore, we here used an intermodal selective attention task with concurrent auditory and visual stimulus streams while recording oscillatory brain activity with MEG. We aimed to (i) replicate earlier findings of deficient motor entrainment in PD patients in conditions where there is a single stimulus stream, and (ii) to evaluate whether increasing the benefit of entrainment by introducing a distractor stream would lead to entrainment in PD patients not seen otherwise. Contrary to this hypothesis, PD patients showed reduced motor entrainment compared to controls during both conditions, as indexed by beta oscillatory activity. These results suggest that entrainment in PD patients is deficient, even under conditions that encourage entrainment.

5.1 Introduction

Low-frequency oscillations have been shown to play a crucial role in perception and action (Gupta and Chen, 2016; Schroeder and Lakatos, 2009). These oscillations are thought to reflect rhythmic fluctuations in excitability of the underlying neural tissue, thereby influencing the likelihood of firing. Several studies have shown that the efficiency of stimulus processing depends on the phase of these slow oscillations (Cravo et al., 2013; Henry and Obleser, 2012). When stimuli possess a certain temporal regularity, the brain optimizes the processing of these stimuli by aligning the phase with high excitability (the preferred phase) with the onset of the external stimuli. This phase-alignment, a process known as neural entrainment, has been shown to take place across different cortical areas and frequencies (Cravo et al., 2013; Gomez-Ramirez et al., 2011; Henry and Obleser, 2012; Lakatos et al., 2008). Entrainment has an additional benefit of helping to suppress irrelevant stimuli that are presented during the low excitability phase (Lakatos et al., 2005, 2008, 2013a). Therefore, in situations where there are multiple stimulus streams, entrainment might serve as a neural process to select and attend the relevant, and suppress the irrelevant stimulus stream.

Entrainment extends beyond the sensory systems, as studies have shown that motor cortical activity can also entrain to external stimuli (Praamstra et al., 2006; Saleh et al., 2010). This entrainment of motor areas has beneficial effects during rhythmic tasks, as it focuses attention and motor readiness to a time window that temporally aligns with stimulus presentation. These findings are in line with the suggestion that rhythmic stimuli can improve motor function, for example during gait, in patients with Parkinson's disease (PD) (Ashoori et al., 2015; Hove and Keller, 2015; Thaut et al., 2015). Behavioural studies support this beneficial effect of rhythmic cues on gait in PD patients (Nieuwboer et al., 2007), but neurophysiological studies have instead shown reduced entrainment of motor areas in PD compared to healthy controls (Praamstra and Pope, 2007; te Woerd et al., 2014, 2015, 2017).

However, previous studies showing this deficient entrainment in PD have only evaluated entrainment in paradigms with one isochronous stimulus stream that still allow for a continuous instead of a rhythmic mode of attending (Schroeder and Lakatos, 2009). In a continuous (vigilance) mode of attending, low frequency oscillations are suppressed and the system is pushed as much as possible into a state of continuous high excitability, allowing fast responses to each presented stimulus (Schroeder and Lakatos, 2009). In conditions where there is more than one (rhythmic) stimulus stream, by contrast, such a continuous mode of attention is detrimental as it can lead to responses to stimuli that have to be ignored. Thus, entrainment is particularly useful in situations where one rhythmic stimulus stream has to be segregated from other (distractor) stimuli (Lakatos et al., 2008, 2013a; Schroeder and Lakatos, 2009; for review see Calderone et al., 2014). Therefore, we hypothesize that, in situations where there are multiple stimulus streams and only one stream is task-relevant, the increased benefit of entrainment might elicit motor entrainment in PD patients, not seen using a single stimulus stream. Such a finding would be in line with earlier evidence that entrainment in PD is context dependent (Cunnington et al., 1999). Cunnington and colleagues used movement-related potentials (MRPs) to show that PD patients have reduced preparatory activity during an externally cued task with temporal regularity, but show normal

entrainment when pointed out that the temporal regularity (the "task rhythm") allows advance preparation.

While the aforementioned evidence suggests that PD patients might deploy entrainment only in challenging conditions, there are also reasons to consider the possibility that the addition of a distractor stimulus stream may have no effect or even be detrimental in PD patients. The bimodal stimulation conditions put a greater demand on internal attentional control, as subjects have to generate and maintain an attentional set for the relevant modality. Studies on attention in PD show that patients are particularly impaired in internal or top-down attentional control, increasing their susceptibility to salient but irrelevant distractors (Brown and Marsden, 1988; Cools et al., 2009; Flowers and Robertson, 1985; Tommasi et al., 2015). Furthermore, internal attentional control also encompasses the generation of temporal predictions by basal ganglia-motor circuits and entrainment of relevant areas to attended external stimuli, a process that has also been shown to be deficient in PD (Grahn and Brett, 2009; Praamstra and Pope, 2007; te Woerd et al., 2014, 2015, 2017). Hence, unaltered or reduced entrainment in bimodal compared to unimodal attention conditions would be consistent with earlier studies showing deficient entrainment in PD, and would indicate deficient oscillatory entrainment as a relevant mechanism underlying changes in attentional control in PD.

We used an intermodal selective attention task with bimodal (auditory and visual) stimulation conditions while recording brain activity using MEG. Different from earlier studies in macaques (Lakatos et al., 2008, 2013a; Schroeder and Lakatos, 2009), which investigated oscillatory activity in sensory cortices, our approach focused on the motor cortex. Firstly, we aimed to replicate earlier findings of deficient entrainment of motor cortex beta oscillations in PD patients in conditions where there is only one stimulus stream. Secondly, we evaluated whether increasing the benefit of entrainment by introducing a distractor stream presented in anti-phase, would lead to better entrainment in PD patients. Based on our earlier work on motor entrainment in PD, analyses focused on entrainment of beta power changes in motor and sensory cortex as the most robust signal showing entrainment by external cues (Praamstra and Pope, 2007; te Woerd et al., 2014, 2015). Note that beta oscillatory power is usually found elevated and of altered responsiveness in PD, with probable pathophysiological significance (for reviews see Brittain and Brown, 2014; Engel and Fries, 2010; Jenkinson and Brown, 2011). The changes in beta activity in PD are improved by dopaminergic therapy and deep brain stimulation (Eusebio et al., 2011; Kühn et al., 2006; Weinberger et al., 2006). Task-related modulations of beta power are therefore a suitable physiological measure to evaluate effects of entrainment.

5.2 Materials and methods

Participants

A total of 12 PD patients (10 men; aged 60 ± 7 years) and 12 healthy subjects (8 men; aged 59 ± 4 years) participated in the experiment. All control subjects were without history of neurological or psychiatric disease. PD patients were of

mild to moderate disease severity (see Table 5.1). All participants provided written consent and the study was approved by the local ethics committee (CMO Arnhem-Nijmegen). All patients were on dopaminergic medication, but the experimental investigation and Unified Parkinson's Disease Rating Scale (UPDRS) rating were performed in the morning, after overnight withdrawal of medication (>12 h). The patient group had a mean score of 23 ± 4 on the motor section of the UPDRS (see Table 5.1) in the OFF state.

Table 5.1 Demographic and clinical characteristics of participating Parkinson patients. UPDRS motor score was determined directly after the experiment. Levodopa was always used with a dopadecarboxylase inhibitor.

Subject number	*Age (yrs) and gender*	*Years since diagnosis*	*Most affected side*	*UPDRS motor score*	*Dominant hand*	*Medication (daily dose)*
1	70, M	6	L	25	R	Levodopa 450 mg Trihexyphenidyl 6 mg Pramipexol 1.5 mg
2	62, M	4	L	25	R	Levodopa 500 mg
3	57, M	5	R	21	L	Levodopa 600 mg
4	67, M	4	L	23	R	Levodopa 450 mg
5	60, F	8	L	19	R	Levodopa 500 mg Ropinirol 8 mg Selegiline 10 mg Amantadine 200 mg
6	48, M	4	R	23	R	Levodopa 500 mg Pramipexol 0.75 mg
7	48, F	4	L	17	R	Levodopa 300 mg Pramipexol 1.125 mg
8	63, M	14	R	27	R	Levodopa 550 mg Pramipexol 3 mg
9	64, M	10	R	31	L	Levodopa 750 mg Entacapone 5x200 mg Amantadine 2x100 mg
10	55, M	4	L	19	R	Levodopa 800 mg Entacapone 800 mg
11	61, M	2	R	20	R	Levodopa 600 mg
12	59, M	17	L	24	R	Levodopa 700 mg Pramipexol 1.5 mg Amantadine 200 mg
Mean (±SD)	60 ± 7	7 ± 5		23 ± 4		

Task and procedure

The experiment consisted of an intermodal selective attention task in which participants had to detect an auditory or visual target during bimodal (auditory and visual) or unimodal conditions (see Figure 5.1). Two of the conditions (auditory unimodal (AU) and visual unimodal (VU)) had only stimuli from one modality and subjects performed a target detection task on the presented stimuli. The other two conditions (auditory bimodal (AB) and visual bimodal (VB)) contained stimuli

from both modalities, with the auditory and visual stimuli presented in anti-phase, and subjects only had to attend to and perform the target detection task in one modality (i.e. in the AB condition subjects attended the auditory stimuli and in the VB condition the visual stimuli). The auditory stimuli (pitch 1000 Hz and 50 ms duration) were presented at a volume of 40 dB above the individual hearing threshold, which was estimated by means of an adaptive staircase procedure before the experiment (Treutwein, 1995). The visual stimulus was a light gray circle presented at fixation for 50 ms, with the circle spanning 1° x 1° of visual angle. A fixation area was permanently indicated by white brackets (enclosing a square of 7.2° x 6.1° of visual angle) surrounding the central screen area where the circle stimuli were presented. All stimuli of the same modality were presented with a fixed stimulus onset asynchrony (SOA) of 800 ms, rendering a fixed presentation rate of 1.25 Hz. Target stimuli were similar to the standard stimuli but with a small reduction in intensity (less volume for the auditory target, and reduced brightness for the visual target), with the detection rate of both targets aimed to be ~80% by means of a four-down/one-up staircase procedure before the experiment (García-Pérez, 1998; Treutwein, 1995). Target probability was 10% for each condition and block, with the targets separated by at least two standard stimuli (both within and between modalities). Participants were instructed to press the response button as swift as possible and first performed a practice block (in each modality) to learn the task. After the practice blocks, stimuli were presented in 12 series of 220 stimuli each (~3 min; three series of each condition), with a short break between series.

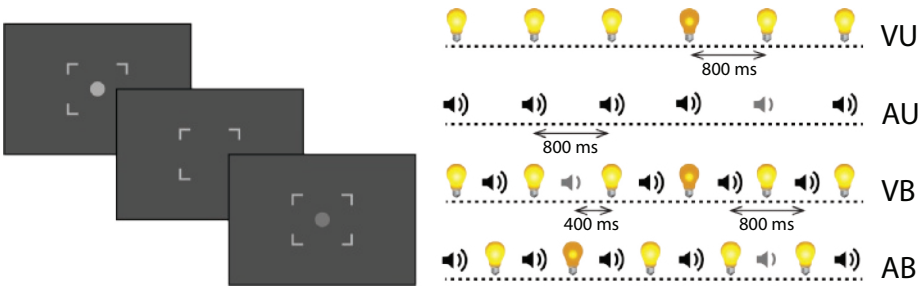

Figure 5.1 Overview of the intermodal selective attention task. There were two types of stimulus streams, an auditory and a visual stimulus stream. In the unimodal conditions, either the visual (VU) or the auditory (AU) stimuli were presented and participants had to depress a button when detecting a target stimulus. In the bimodal conditions, the auditory and visual stimulus streams were presented simultaneously but in anti-phase, and participants had to attend either to the visual (VB) or to the auditory (AB) stimuli. Targets were defined by a lower intensity.

MEG recordings

Ongoing brain activity was recorded using a whole-head MEG system with 275 axial gradiometers (VSM/CTF Systems, Coquitlam, BC) in a magnetically shielded room. During the experiment, we continuously measured head position relative to the sensor array using localization coils that were placed at the nasion and in the left and right ear canals (Stolk et al., 2013). Vertical electro-oculogram (EOG) was recorded from the supra- and infraorbital ridges of the left eye, and horizontal EOG from the bilateral outer canthi. MEG and EOG data were sampled at 1200 Hz.

Behavioural analyses

Reaction time analyses were performed on the responses to the target tones, after excluding trials in which the response exceeded a reaction time cut-off (>900 ms). Mean response times were determined for each condition (AU, VU, AB, and VB) separately. In addition, we calculated the overall percentage of detected targets (percent correct) and percentage of correct rejections (not responding to targets in the unattended stream in the bimodal conditions).

MEG data analyses

MEG data were analyzed with MATLAB 2014a (Mathworks, Natick, MA) using the open-source FieldTrip toolbox (Oostenveld et al., 2011). For the main analyses, epochs of 5000 ms (2500 ms pre-stimulus and 2500 ms post-stimulus) were extracted from the continuous data separately for all conditions. These epochs all consisted of four consecutive standard stimuli, using series of non-target stimuli and no button responses to avoid any movement-related activity. After removal of trials containing muscle artifacts, slow drift, or SQUID (superconducting quantum interference device) jumps, data were down-sampled to 400 Hz.

Independent component analysis was used to remove any remaining variance caused by eye blinks and heartbeat artifacts. As an extra check, the remaining data epochs were visually inspected and any epochs with artifacts were removed manually. The remaining stimulus-locked epochs were submitted to time-frequency and statistical analyses. Statistical analyses were performed with the factors Group (controls vs. patients), Condition (unimodal vs. bimodal stimulus presentation), Modality (auditory vs. visual stimuli) and Attention (attended vs. unattended stimuli in the bimodal conditions). All statistical analyses presented here were performed using SPSS version 19 (IBM Corp. Armonk, NY) unless stated otherwise.

Event-related fields

Before calculating the event-related fields (ERFs), all data were low-pass filtered using a 6th-order two-pass Butterworth filter with a cut-off frequency of 30 Hz. ERFs were baseline corrected by subtracting the mean signal amplitude in the 100 ms pre-stimulus interval (-100 - 0 ms). A planar gradient transform was subsequently calculated (Bastiaansen and Knösche, 2000), which simplifies the interpretation of the sensor-level data by placing the maximal signal above the source.

Time-frequency analyses

Frequency decomposition was performed on the horizontal and vertical components of each axial channel, after which these components were combined to obtain the oscillatory power at each synthetic planar channel. For all channels, time-frequency representations (TFRs) were calculated using a Fourier transform approach, applied to short sliding time windows across the entire length of the epochs, with a step-size of 10 ms. Before the Fourier transform, the data in each time window was

tapered with a Hanning function. The mean planar gradient power was estimated for all trials within a condition in the frequency range 1-30 Hz (1 Hz frequency resolution) and an adaptive time window of four cycles for each frequency. For the main analyses, percentage change in oscillatory power was defined as the relative change with respect to the mean power in the epoch (-1000 to 1200 ms post-stimulus time window). Statistical analyses of TFRs were performed in the Fieldtrip toolbox (Oostenveld et al., 2011) by means of a cluster-based permutation test with 1000 randomizations over the whole epoch length (-1 to 1.2s post-stimulus) and over all frequencies (1 to 30 Hz).

5.3 Results

Behavioural data

Participants had to detect auditory or visual deviants amidst a stream of standard stimuli, and these auditory and visual streams were either presented separately (unimodal conditions: AU and VU) or simultaneously but in anti-phase (bimodal conditions: AB and VB). Across groups, detection rate of the deviant stimuli was lower for the visual than for the auditory domain, as shown by a main effect of Modality ($F_{1,22} = 42.2$, $p < 0.001$) (Figure 5.2A). This difference between modalities was larger for the patient than for the control group, as indicated by an interaction between Modality and Group ($F_{1,22} = 6.2$, $p = 0.021$). Presentation of a concurrent distractor stream in anti-phase significantly worsened detection rate across groups ($F_{1,22} = 65.0$, $p < 0.001$). This negative effect of the distractor stream was larger in the auditory than in the visual domain, as indicated by an interaction between Modality and Condition ($F_{1,22} = 7.8$, $p = 0.011$). Overall detection rate was not different between groups ($F_{1,22} < 1$), nor was there an interaction between Group and Condition ($F_{1,22} < 1$). The three-way interaction between Condition, Modality and Group approached significance ($F_{1,22} = 4.0$, $p = 0.058$), due to a stronger interference by the distractor stream in the visual modality for patients. Both groups were equally able to selectively attend the relevant stream in the bimodal conditions, as false alarms, i.e. responses to deviants in the unattended stream, was at floor level in both the auditory (controls: 1 ± 2%; patients 1 ± 2%) and visual (controls: 1 ± 2%; patients: 1 ± 1%) conditions.

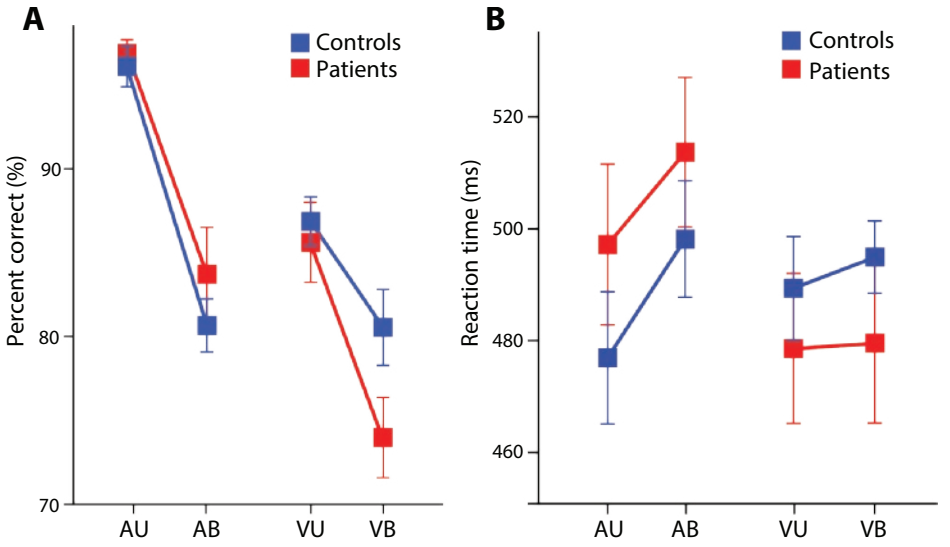

Figure 5.2 Behavioural data for both groups and all conditions. A) Percentage of targets that were detected correctly. B) Average response time to targets. Whiskers represent the standard error.

Overall response times to deviant stimuli were not significantly different between groups ($F_{1,22} < 1$) (Figure 5.2B), and not significantly different between the auditory and visual domain ($F_{1,22} = 1.9$, $p = 0.18$). Presentation of the concurrent distracting stimuli significantly delayed response time, as shown by a main effect of Condition ($F_{1,22} = 16.8$, $p < 0.001$). This effect of the distractor stream was larger for auditory than for visual targets, indicated by an interaction between Modality and Condition ($F_{1,22} = 8.9$, $p = 0.007$). The interaction between Modality and Group approached significance, suggesting faster response times for controls than patients in the auditory domain, but vice versa in the visual domain ($F_{1,22} = 3.9$, $p = 0.060$). There were no further interactions involving the factors Modality, Condition or Group.

Attentional modulation of neural responses

We analyzed the magnetic field in response to auditory and visual stimulation in two regions of interest overlying the auditory and visual cortices, with each region of interest (ROI) consisting of 20 sensors (10 per hemisphere and symmetrically distributed over hemispheres, see Figure 5.4). These sensors showed, averaged across groups and relevant conditions (i.e. AU and AB for auditory ROI), the strongest magnetic response to the presented stimuli. The auditory and visual stimuli both produced a large neural response in the ERF, reaching a maximum peak at approximately 150 ms post-stimulus for both modalities and groups (Figure 5.3). The amplitude of the N1-response was, for the unimodal conditions, not different between groups ($F_{1,22} < 1$) or modalities ($F_{1,22} < 1$). In the bimodal conditions, there was a significant enhancing effect of Attention on N1-amplitude ($F_{1,22} = 26.1$, $p < 0.001$). This effect of attention was larger for the visual than for the auditory domain, as shown by an interaction between Attention and Modality

(F1,22 = 11.9, p = 0.002). There were no further effects or interactions involving the factors Modality, Group or Attention.

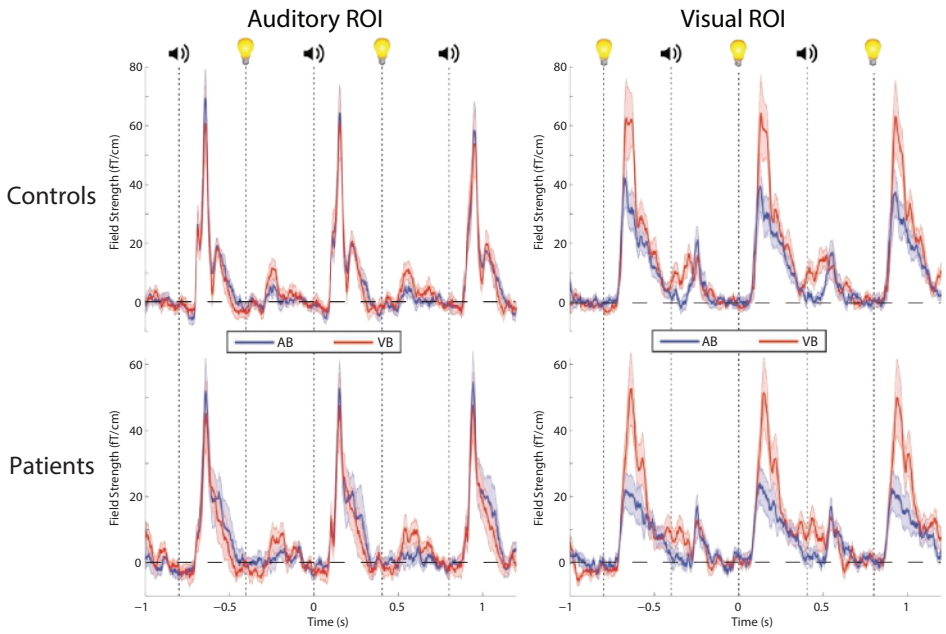

Figure 5.3 Evoked fields over the auditory and visual ROIs for both groups, in the bimodal conditions. The two left panels (top: controls, bottom: patients) show the magnetic field strength over the auditory ROI in the AB (blue) and VB condition (red) time-locked to the onset of the auditory stimuli. Panels on the right show the magnetic field strength over the visual ROI in the same conditions, time-locked to the onset of the visual stimuli.

To gain more insight into the effects of attention on neural processing, we calculated time/frequency representations (TFRs) of the changes in magnetic field strength over the sensory ROIs and, as we want to investigate motor entrainment, over a region of interest overlying the motor cortex contralateral to the response hand (Figure 5.5A). This motor ROI consisted of 10 sensors that showed the strongest neural response after target stimuli, averaged across groups and all conditions. This analysis showed strong spectral power changes in predominantly the theta (4-8 Hz) and beta (13-30 Hz) frequency-bands (Figure 5.4), for all ROIs and groups. The strongest attentional effects were seen in spectral power changes in the beta frequency-band, with power changes significantly stronger for the attended than for the ignored stimulus stream for both groups and all ROIs ($p < 0.05$). However, beta power changes were not different between attended and ignored streams over the motor ROI for PD patients, and we will zoom in on this differential result in the following sections.

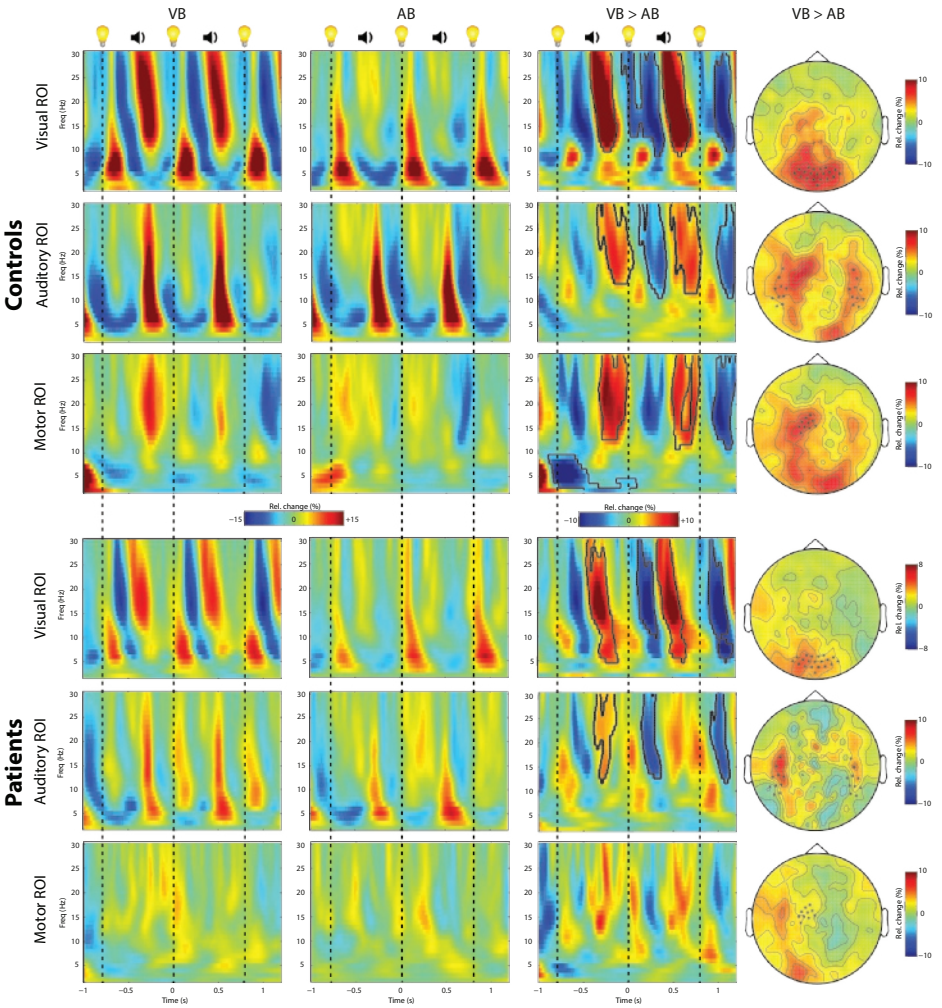

Figure 5.4 Time-frequency representations of the changes in magnetic field strength over the visual, auditory and motor ROIs in the AB and VB conditions (time-locked to visual stimulus presentation). Dashed lines indicate time of visual stimulus presentation. In the third column, black solid lines surround time-frequency clusters that contribute to the significant difference ($p < 0.05$) between conditions. Topographies on the right show spatial properties of the significant ERS-clusters between conditions (stars indicate sensors of the visual, auditory and motor ROIs). Since there was no significant effect for patients over the motor ROI, the topography is represented over the same time window and frequency range as for controls, to allow a comparison.

Deficient motor entrainment in Parkinson's disease

Participants were instructed to depress the response button as swiftly as possible when detecting a deviant stimulus in the attended stream, requiring response readiness at the regularly spaced times of stimulus occurrence. We evaluated this induced motor entrainment by examining beta (13-30 Hz) oscillatory power changes. As expected, the results showed the strongest spectral power changes

in this frequency band. To estimate entrainment strength, beta power modulations were calculated for all conditions (Figure 5.5B), after which we took the absolute of these traces and calculated the area under the curve for the entire epoch (1000 ms pre-stimulus to 1200 ms post-stimulus). Entrainment of motor cortex beta power was significantly reduced in PD patients compared to controls during unimodal stimulation, as indicated by a main effect of Group ($F_{1,22} = 6.0$, $p = 0.023$) (Figure 5.5C). There was no difference between modalities ($F_{1,22} < 1$), and no interaction between Group and Modality ($F_{1,22} = 1.7$, $p = 0.20$). Similar analyses over the sensory ROIs showed a strong effect of Modality ($F_{1,22} = 35.9$, $p < 0.001$), but no difference between groups ($F_{1,22} = 2.1$, $p = 0.17$) and no interaction between Group and Modality ($F_{1,22} < 1$) (Figure 5.5D). These differential results over sensory and motor ROIs are in line with our earlier finding of a reduced engagement of motor areas in PD patients during rhythmic tasks using a single stimulus stream, with no differences between groups over sensory areas (te Woerd et al., 2017). The current results additionally show that this effect is not modality specific, as the reduced entrainment is found for the attend auditory and for the attend visual target conditions. However, despite the differential results over sensory and motor ROIs, a direct test of an interaction between ROI and Group was not significant in the current study ($F_{1,22} = 2.9$, $p = 0.10$). Possibly, the lack of an interaction between Group and ROI is related to the faster stimulation rate reducing the beta power modulation in the sensory cortices more in patients than in control subjects (see Figure 5.5D).

We performed similar analyses with respect to beta oscillatory entrainment for the bimodal conditions (Figure 5.5C). Adding the stream of distractor stimuli did not elicit stronger entrainment in either group as there was no main effect of Condition ($F_{1,22} = 1.8$, $p = 0.19$), and did not lead to normal entrainment in PD patients as indicated by a main effect of Group ($F_{1,22} = 6.3$, $p = 0.02$) and the absence of an interaction between Group and Condition ($F_{1,22} = 1.4$, $p = 0.25$). There were no further interactions between Group, Condition and Modality.

In order to verify the behavioural relevance of beta entrainment, we hypothesized that stronger engagement of motor areas, as indexed by entrainment, would lead to more responsiveness (since motor readiness is higher and resources are available at the appropriate time) and thus a higher hit rate. Therefore, we tested for a correlation between entrainment strength and hit rate of the deviants. There was a significant correlation between beta entrainment and hit rate in the control group ($r = 0.41$, $p = 0.004$), with stronger entrainment being related to a higher hit rate. Such a correlation between beta entrainment and hit rate was absent in the patient group ($r = -0.07$, $p = 0.61$). We also tested whether there was a within-subject correlation between entrainment strength and hit rate, but could not find strong evidence for such a correlation.

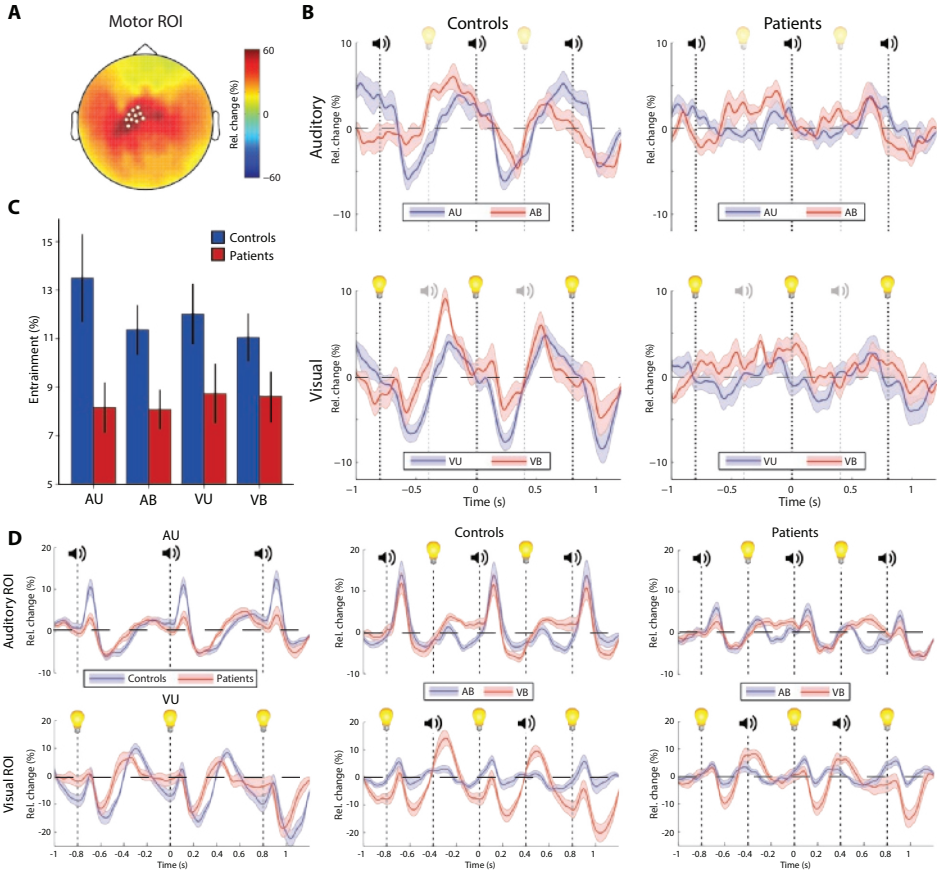

Figure 5.5 A) Sensors used as the region-of-interest for analyzing motor activity. The topography shows beta power modulation, contrasting beta ERD and ERS phases after button press. B) Beta power over time for the sensors in the motor ROI in the AU, AB (top) and VU and VB (bottom) conditions. Note that the (distractor) stimuli, depicted in light grey at 400 ms pre- and post-stimulus, are only presented in the bimodal conditions. C) Mean area under the curve as an estimate for entrainment strength, for all conditions and groups. D) Beta power traces over the auditory and visual ROIs for all conditions and both groups.

To follow up on this differential result for controls and patients, we hypothesized that the reduced beta entrainment in patients does not have to be detrimental to behaviour if these smaller beta power modulations do correctly phase-entrain to the rhythm of the attended stream. We calculated entrainment of beta oscillations in an alternative way, namely by estimating the instantaneous phase of contralateral beta power changes (from the Hilbert transform of the signal filtered around the stimulation frequency) at stimulus onset (Figure 5.6B). These analyses showed a significant phase preference at stimulus onset for controls, as tested by means of Rayleigh's test for non-uniformity of phase data ($p < 0.025$ for all conditions). Similar analyses for the patient group only showed a significant phase preference for the AU and AB conditions ($p < 0.043$ in Rayleigh's test).

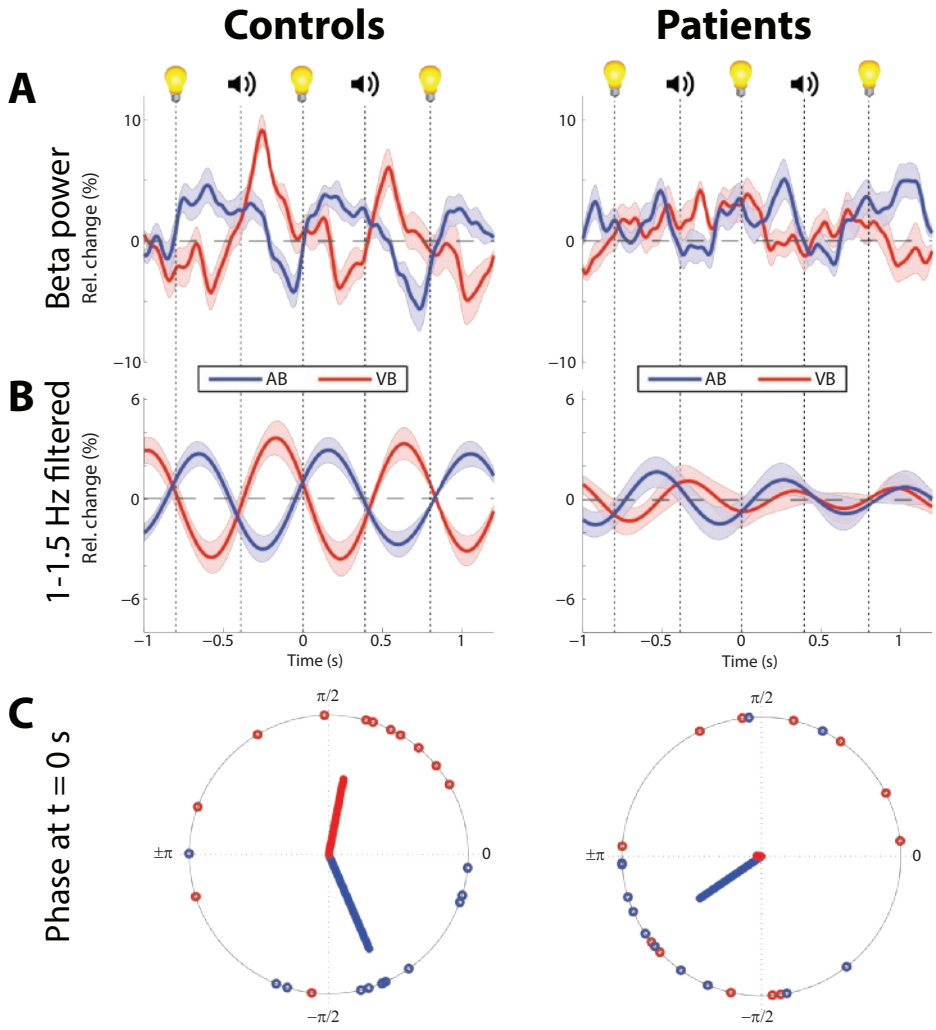

Figure 5.6 A) Beta power over time in the sensors of the contralateral motor ROI in the bimodal conditions (AB and VB), represented in visual-locked fashion. B) Similar to A, but now with the beta power traces filtered around the stimulation frequency of 1.25 Hz. C) Instantaneous phase of the beta power traces for all individuals represented as dots at edge of circular plots, and the resultant vector in the centre. Longer vector length shows stronger phase consistency across individuals, angle of the vector shows the mean phase angle. Red is used for the VB condition, blue for the AB condition.

Importantly, the aforementioned definitions of entrainment are only indicative of phase consistency but do not give information on the specific phase angle. Since the bimodal conditions contain auditory and visual stimuli presented in anti-phase, one would expect phase opposition of beta power changes at stimulus onset when comparing the AB and VB conditions. Interestingly, when directly comparing the mean phase angles between the AB and VB conditions at the onset time of visual stimuli, there was a significant phase-difference between conditions for the control group only ($p = 0.014$, Figure 5.6C). A similar phase-difference between conditions

was found for controls when comparing the AB and VB conditions in an auditory-locked fashion ($p = 0.041$). This was not the case for the patient group, with the phase at stimulus onset being no different between the AB and VB conditions in both the visual locked ($p = 0.68$) or the auditory-locked ($p = 0.10$) analyses. These results show that in healthy controls the motor cortex is actively tracking the rhythm of the attended stream, while this process is impaired in PD patients.

5.4 Discussion

In this study, we used an intermodal selective attention task to investigate selective entrainment of oscillatory brain activity in a group of PD patients and a healthy control group. The results show that i) both groups were equally able to detect targets in the isochronous streams of stimuli, ii) attention enhances the neural response to attended stimuli over sensory areas for both groups equally, and iii) that increasing task difficulty due to competing stimulus streams does not elicit motor entrainment in PD patients like in healthy controls, neither in terms of beta power fluctuations, nor in terms of selective beta power phase-entrainment. We will discuss the implications of these findings with respect to the role of oscillatory entrainment in selective attention, sensory-motor interactions during rhythmic tasks, and the use of rhythmic stimuli in the rehabilitation of PD patients.

Studies have shown that oscillatory activity has an important role in numerous brain functions and processes, and an example of this is the strong influence of oscillatory activity on attentional processing (for review see Gregoriou et al., 2015). Neural oscillations are capable of promoting or suppressing the detection of external stimuli (Henry and Obleser, 2012; VanRullen et al., 2011), as they reflect the excitability of the neural tissue in which they occur (Lakatos et al., 2005; Steriade et al., 1993). Findings such as these have led to the idea that the brain uses oscillations to focus neuronal excitability to time points at which external stimuli are expected and facilitate their processing in both sensory and motor areas. This alignment of neural oscillations with external stimuli, i.e. oscillatory entrainment, may be related to behavioural entrainment phenomena and is subject of theories on (rhythmic) attentional processing such as the Dynamic Attending Theory (Jones, 1976; Large and Jones, 1999).

The positive effects of neural entrainment on the motor system are in line with behavioural studies showing that rhythmic stimuli (or cues) facilitate motor function in PD patients (for reviews see Ashoori et al., 2015; Lim et al., 2005; Spaulding et al., 2013). However, evidence regarding the neurophysiology underlying these positive effects is still unclear and, moreover, there is even evidence that PD patients are less sensitive to temporal regularities than control subjects (Grahn and Brett, 2009). We hypothesized that neural entrainment could be the neurophysiological process that underlies these positive effects, but found reduced entrainment of oscillatory activity in PD patients instead (te Woerd et al., 2014, 2015, 2017). However, this reduced entrainment might also be due to the fact that in previous studies, we only used one single stimulus stream which did not require entrainment per se. In such conditions, similar to the AU and VU conditions of the current study, the

brain can use a continuous mode of operation (Schroeder and Lakatos, 2009), allowing fast responses to each presented stimulus. In conditions where there is more than one (rhythmic) stimulus stream, like the AB and VB conditions, such a continuous mode of attention is detrimental as it can lead to responses to stimuli that have to be ignored. In such situations entrainment is particularly useful, as it can serve as a temporal filter that speeds processing in specific time windows (those when attended stimuli are expected), and suppresses all input between those time windows (Horton et al., 2014; Lakatos et al., 2008, 2013b; Zion Golumbic et al., 2013). Note that the evidence for an attentional role of slow oscillations was primarily obtained in macaque studies with recordings in primary sensory (auditory and visual) cortex (Lakatos et al., 2005, 2008, 2013a). However, in one human study with recordings of intracranial electrocortical activity during an intermodal attention task, the motor cortex was among regions exhibiting the most robust and reliable entrainment effects (Besle et al., 2011), thus supporting our approach.

Relevant to the notion that a more challenging task might elicit entrainment not seen in an easy task, there are studies showing that tonic levels of dopamine in the striatum alter the threshold for allocating physical resources (energizing behaviour) and thereby bias cost-benefit decision-making processes about whether to exert physical effort to obtain reward (Collins and Frank, 2014), with an opposite role for serotonin in modulating the drive to withdraw behaviour (Tops et al., 2009). This means that the level of tonic striatal dopamine promotes physically effortful response vigour: the higher the level of tonic dopamine, the higher the expected reward rate, and the more costly it is to delay motor responding (Beierholm et al., 2013; Dayan, 2012; Guitart-Masip et al., 2011; Niv et al., 2006, 2007). This has led to the proposal that the dopaminergic projection to the striatum provides a signal for implicit “motor motivation” (Mazzoni et al., 2007). This notion is in line with work showing that the striatum functions as a node that regulates motivation of mental and physical effort (Schmidt et al., 2012). A high level of dopamine would then lead to more effort being invested for an identical amount of reward, which is confirmed by studies in hyperdopaminergic rats (Beeler et al., 2010; Nunes et al., 2010). Conversely, studies in PD patients with a low level of dopamine, have indeed found that patients show an implicit decision to invest less effort in a movement compared to healthy controls because of a shift in the cost / benefit ratio of the energy expenditure (Chong et al., 2015; Mazzoni et al., 2007), with PD not affecting the speed-accuracy trade-off.

The emerging view of a role of the basal ganglia in modulating “motor motivation” (see also Turner and Desmurget, 2010) is especially relevant to the present work, given the evidence that entrainment of beta power is engaged in an effort-dependent manner, increasing with task difficulty (Lakatos et al., 2013b). The results of our experiment, however, were convincingly clear in showing that increased task difficulty, in the form of a competing stimulus stream in an intermodal attention task, does not improve impaired entrainment of motor cortical beta oscillatory power in PD. One could see the fact that also controls did not show stronger entrainment in the bimodal versus unimodal conditions as a possible limitation of the current study. It is therefore important to note that, in controls, the unimodal conditions already instantiated a proper level of automatic entrainment that is also likely to be sufficient

for the bimodal conditions. However, in PD patients, the unimodal conditions do not elicit automatic entrainment (Praamstra and Pope, 2007; te Woerd et al., 2014, 2015, 2017) and, based on aforementioned findings on motor motivation and beneficial effects of entrainment, the main goal was to test whether increased task difficulty does elicit more normal entrainment in PD patients. The important result here is therefore that motor entrainment in PD patients is deficient, even in situations that encourage entrainment, while controls show proper rhythmic entrainment in both conditions.

The severely deficient entrainment of motor cortex beta power in PD patients raises the question why they were not worse than controls in their performance. The lack of group differences in behavioural outcome might be explained by the task still being sufficiently easy to be performed in a continuous attention mode instead of a rhythmic mode. Note, however, that there was a significant performance difference between the groups, after all. Only in controls the strength of entrainment correlated with target hit rate. This would predict that with further increased difficulty of the task, PD patients' performance might well break down. The reduced motor entrainment raises also questions regarding the contribution of the basal ganglia-motor system in attentional control. Motor circuits and the basal ganglia play an important role in internal rhythm generation and the formation of temporal predictions (Bartolo et al., 2014; Grahn and Rowe, 2009, 2013; Teki, 2014), and it has been suggested that these temporal predictions are coded in beta oscillatory activity (Arnal, 2012; Bartolo et al., 2014; Gulberti et al., 2015). Studies have shown that these temporal predictions are being sent back to sensory areas, and can alter the processing of sensory stimuli (Morillon et al., 2014, 2015). Against this background, the deficient rhythm generation in the basal ganglia-motor system of PD patients could have led to differences in sensory processing between the two groups. However, neither behavioural nor analyses of visual and auditory evoked and oscillatory activity yielded such evidence. A potential explanation might be the fact that in the current study participants made motor responses only to infrequent targets. Morillon and colleagues (2014) showed that top-down effects of the motor system on sensory processing were markedly influenced by actual rhythmic motor behaviour.

Conclusion

This work shows that PD leads to deficient entrainment of motor areas during tasks containing rhythmic stimuli, even in situations that encourage entrainment. This deficient motor entrainment is expressed in beta oscillatory power changes, not only in the modulation depth, but also in the phase of beta power changes. These changes in oscillatory power modulations are likely a reflection of impaired basal ganglia activity required for internal rhythm generation. This finding reflects on the use of rhythmic cueing in rehabilitation of PD patients, as they extend earlier evidence that rhythmic stimulation in PD fails to engender a predictive mode of motor activation, as it does in healthy controls.

General discussion

6.1 Summary

Our brains can perceive and produce rhythms of different tempi, and often when we perceive a rhythm in the environment, our brains entrain to this rhythm to achieve several advantages such as improved motor performance. Based on this concept, rehabilitation of patients with Parkinson's disease (PD) makes use of rhythmic cueing. However, internal rhythm production in PD patients is believed to be disrupted and patients have been shown to be less sensitive to external rhythms; yet they benefit from cueing approaches. The aim of this thesis was to address this apparent paradox, by investigating the neurophysiology of cueing in PD from an oscillatory perspective. In this General Discussion, I will summarize the most important findings of the previous chapters and discuss them in light of the physiology of neural entrainment and its role in (temporal) prediction and attention. I will then present a new perspective on the physiology of cueing, by integrating the findings presented in this thesis, with current ideas on neural and motor entrainment.

I have performed four studies to investigate the neurophysiology of cueing in PD, and each study contributed information on oscillatory entrainment and how (rhythmic) cues can or cannot improve motor function. In each study, I used MEG to record oscillatory brain activity in a group of PD patients and a control group of healthy volunteers. The main findings of these studies are:

1. Despite similar behavioural outcomes as healthy subjects, PD patients demonstrate a shift from predictive to reactive beta modulation (chapters 2 and 3).
2. PD patients show less delta phase synchronization than controls, alongside delayed gamma power synchronization. The delta phase synchronization is correlated with the magnitude of predictive beta modulation (chapter 2).
3. Rhythmic stimuli lead to an increase of the beta modulation depth, and they do this to the same extent in both patients and controls, possibly facilitating movement (chapter 3).

6

4. The increase in beta modulation depth is solely due to an increase in the beta event-related synchronization (ERS) phase, increasing the predictive beta modulation (chapter 3).
5. Similar to control subjects, patients process movement-likelihood information adequately in sensory areas, but subsequent motor preparation is reduced in PD patients (chapter 4).
6. Reduced entrainment of beta power changes in PD is confined to motor areas only, leaving sensory entrainment intact (chapters 4 and 5).
7. Motor entrainment in PD patients is reduced, even in situations that encourage entrainment (chapter 5).

Below I will discuss and contextualize these findings in two main sections; the role of oscillatory entrainment in attention and prediction, and the neurophysiology of cueing in PD.

6.2 Role of oscillatory entrainment in attention and prediction

The brain has to deal with an enormous amount of incoming information, and there are not enough resources to process all input. Fortunately, several mechanisms are in place to filter incoming information by separating relevant from irrelevant input. Two complementary mechanisms that help the brain to process incoming information are attention and prediction (Summerfield and Egner, 2009). Prediction influences stimulus processing based on prior likelihood (for review see Summerfield and De Lange, 2014), and attention modifies stimulus processing on the basis of behavioural relevance (for reviews see Corbetta and Shulman, 2002; Kastner and Ungerleider, 2000). Both processes, and their interactions (Nobre et al., 2007), lead to more efficient detection and recognition of behaviourally relevant stimuli. An example of this was presented in **chapter 4**, where stronger predictions of an upcoming target tone decreased response time. Attention and prediction appear to be (partially) implemented in oscillatory activity by means of two mechanisms, namely the resetting or entrainment of oscillatory phase (Herrmann and Henry, 2014) and changes in oscillatory power (for reviews see Frey et al., 2015; Gregoriou et al., 2015; Morillon and Schroeder, 2015). Since neural oscillations signal the rhythmic shifting between relatively depolarized and hyperpolarized states of the underlying neuronal tissue, there appears to be a relationship between the EEG/MEG signal measured at the scalp and neuronal excitability (Bishop, 1932; Buzsáki, 2006; Buzsáki et al., 2012; Lakatos et al., 2005; Lopes da Silva, 2013; Vanhatalo et al., 2004). Here, I will discuss how the results of the previous chapters contribute to current understanding of the functional role and physiology of oscillatory entrainment in sensory and motor areas of the brain, and to current ideas of oscillatory processes underlying attentional and predictive processing.

Entrainment of slow (ongoing) oscillations

Since neural excitability, reflected (at least partly) in neural oscillations, fluctuates over time, incoming stimuli are not always processed similarly. This is confirmed by studies showing an effect of ongoing oscillatory activity on sensory processing (Arieli et al., 1996; Fries et al., 2001). That is, in the cycle of an oscillation there is a phase at which excitability is high (the 'ideal' phase) and a phase during which excitability is low (the 'worst' phase) (Lakatos et al., 2005). A stimulus that arrives during the ideal phase leads to amplified evoked activity and is most likely detected, whereas a stimulus that is presented during the worst phase generates significantly less evoked activity and might be missed (Fries et al., 2002; Lakatos et al., 2005, 2007; Volgushev et al., 1998; Womelsdorf et al., 2006). In short, particularly in situations when stimuli are near the threshold of detection, oscillatory phase determines whether or not a stimulus is detected and reaches consciousness (Henry and Obleser, 2012; Mathewson et al., 2010).

The influence of neural oscillations on stimulus processing has led to several theories that relate oscillatory activity to (temporal) prediction (Arnal and Giraud, 2012; Barne et al., 2017; Morillon and Schroeder, 2015) and attention (for review see Nobre and Van Ede, 2018), such as the inhibition-timing (Klimesch et al., 2007), the gating by inhibition (Jensen and Mazaheri, 2010) and the oscillatory selection hypothesis (Schroeder and Lakatos, 2009). The latter hypothesis suggests that

ongoing oscillatory activity forms the "context", which affects processing of sensory input (the "content") (Buzsáki and Chrobak, 1995; Lakatos et al., 2009). A number of studies have shown that there is a two-way interaction between the context and the content (Kayser et al., 2009; Lakatos et al., 2007, 2008). Namely, besides ongoing oscillations having an effect on the processing of sensory input, the sensory input can influence ongoing oscillations by means of resetting the oscillatory phase (Basar, 1980; Sayers et al., 1974). By this phase reset, ongoing oscillations can become entrained to rhythmic external events that are behaviourally relevant (Kayser et al., 2009; Lakatos et al., 2008), a process largely influenced by attention (Lakatos et al., 2005). In addition, it is important to mention that this oscillatory synchronisation (entrainment) can establish itself automatically in rhythmic environments. On a side note, while I am discussing specifically the entrainment of neural oscillations with external stimuli in this thesis, the phase-alignment can also take place between two neuronal areas. Specifically, such a process is described in the "communication through coherence" theory, which posits that two neuronal populations can communicate most effectively when their oscillatory phases are aligned (Fries, 2005). Delta-band oscillations are thought to have a particularly important role in this process, as their phase synchronization is thought to dynamically link neurons into functional networks (Womelsdorf et al., 2007; Womelsdorf and Fries, 2006).

A prerequisite for entrainment is phase reset, which ensures that ongoing oscillations can be realigned to rhythmic external events and allow a predictive rather than reactive processing mode (Lakatos et al., 2008; Large and Jones, 1999; Schroeder and Lakatos, 2009). The nature of entrainment as a predictive process is supported by the finding that entrained oscillations can outlast the external stimulation (Lakatos et al., 2013a; Spaak et al., 2014). In **chapter 2** I investigated this predictive nature of oscillatory entrainment by contrasting a condition that allowed only temporal preparation with a condition allowing both temporal and effector preparation. All stimuli in **chapter 2** were presented rhythmically and allowed for entrainment of delta oscillations. The addition of effector predictability led to stronger delta entrainment in both controls and patients, with an interaction between hemisphere and condition. That is, besides the overall stronger entrainment, the predictable condition allows the brain to optimize processing in the relevant hemisphere for the upcoming stimulus, while decreasing excitability in the other hemisphere. While I did not test this effect, it would be interesting to test for a difference in phase angles between contra- and ipsilateral hemispheres during both conditions in **chapter 2**. Such an analysis should reveal no phase difference between hemispheres in the random condition as both sides need to be prepared, while there should be phase opposition in the predictable condition (Figure 6.1A). Namely, entrainment not only increases excitability within stimulus- and task-relevant regions at specific points in time, but also sharpens the representation of attended stimuli by down-regulating the excitability of stimulus- or task-irrelevant ensembles (Lakatos et al., 2013a, 2013b), incorporated by the sign of the phase reset (O'Connell et al., 2011).

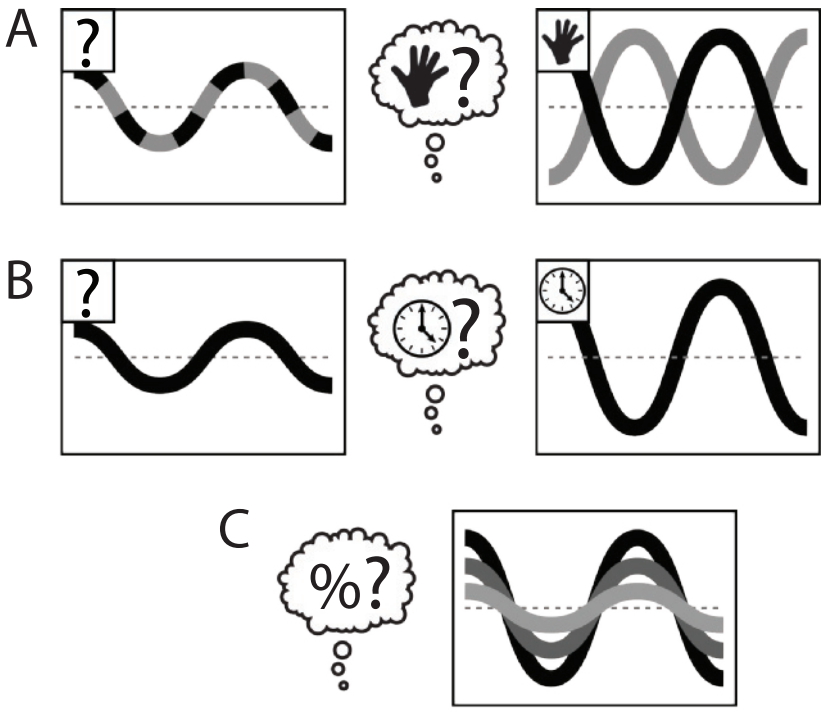

Figure 6.1 Schematic overview of ways in which delta phase entrainment can modulate stimulus processing and motor readiness. A) As shown in chapter 2, when the upcoming effector is uncertain, entrainment is equal (in strength and phase) for both the ipsi- (grey line) and contralateral (black line) hemisphere (left panel). Effector predictions cause overall stronger motor delta phase entrainment with opposite phases across hemispheres (right panel). B) In situations where stimulus timing is uncertain, delta phase entrainment is low in order to maintain a more continuous processing mode (left panel). However, when stimulus timing is predictable, temporal predictions increase phase synchronization and enhance processing and motor performance in specific time windows as shown in chapter 3 (right panel). C) In chapter 4 I showed that the effect of (temporal) predictions on delta phase entrainment is not an on/off-process, but that predictions vary in strength and that therefore the strength of delta phase entrainment is gradually modulated.

Whereas oscillatory entrainment can be useful when stimulus timing is predictable, the cost is "downtime" and inputs arriving during the low-excitability phase might be missed (Mathewson et al., 2010). This is in line with the notion that attending to a particular point in time enhances perception at that time, but decreases perception in earlier and later time windows (Denison et al., 2017). Therefore, in situations where it is uncertain when a stimulus will appear, slow (delta) oscillations can actually be detrimental to behaviour. In such situations, attention enforces slow oscillations to be suppressed and thereby initiate a continuous processing mode (Fries et al., 2001; Lakatos et al., 2008; Schroeder and Lakatos, 2009). This difference between rhythmic and non-rhythmic situations was the topic of **chapter 3**, where I contrasted conditions with either rhythmic or non-rhythmic stimuli. The results indeed showed stronger delta phase entrainment in rhythmic conditions (Figure 6.1B), and only in these situations there appeared to be a strong functional role of entrained delta oscillations given the correlation with response time (**chapter 3**). It is important to mention that rhythmic and continuous processing modes are most

likely simultaneously active during most tasks, but to different degrees depending on the temporal predictability of the input (Frey et al., 2015). Moreover, the continuous processing mode is difficult to maintain for longer periods and is often shortly interrupted by lapses into rhythmic mode processing (Henry and Herrmann, 2012), providing an explanation for the finding that even in continuous mode processing delta phase predicts target detection performance (Ng et al., 2012).

The results of **chapters 2 and 3** are in line with the suggestion that (temporal) prediction and attention might use delta phase entrainment as a means to optimize processing in relevant brain areas. It is worth mentioning that the temporal expectancies, generated by rhythmic stimulus presentation can work in parallel to any temporal expectancies generated by the simple passage of time (foreperiod effect) (Jones et al., 2017). Where in **chapter 2** delta phase entrainment was dynamically implemented to bring the relevant hemisphere(s) into an optimal state at the appropriate time, in **chapter 3** delta phase entrainment was implemented to optimize processing at the predicted onset time of stimuli. However, multiple studies have shown that prediction functions on a continuous scale as one can have weak or stronger predictions (Stefanics et al., 2010). The stronger these predictions, the more the brain is biased towards them and any violations of these predictions are more detrimental. This is also demonstrated in the response times to deviant SOAs in **chapter 2**, where violations of temporal predictability were more disruptive when not only the stimulus timing was predicted but also the effector. The increased response times to stimuli presented out of the predicted rhythm, can be seen as manifestations of entrainment (Jones et al., 2017). Interestingly, this disruptive effect of deviant SOAs was equal for both healthy controls and PD patients, suggesting intact predictions in patients. This finding of reduced preparatory activity but intact encoding of time intervals replicates earlier findings (Jurkowski et al., 2005; Praamstra and Pope, 2007).

To zoom in on this relation between prediction strength and oscillatory changes, I used rhythmic auditory stimuli in **chapter 4**. The pitch of these tones predicted target likelihood, and rhythmic stimulus presentation allowed oscillatory entrainment in auditory and motor areas. The predictive nature of oscillatory entrainment was demonstrated by clear delta phase entrainment at the time a stimulus was expected, but omitted. Additionally, it is important to mention that I tested two varieties of predictions in **chapter 4**, namely (i) the rhythmic stimulus presentation was used to test whether the overall temporal predictability could lead to entrainment of motor cortical delta oscillations induced by auditory stimuli, and (ii) whether a more 'discrete' form of prediction, induced by the target-likelihood that varied on a trial-to-trial basis, could modulate the strength of delta phase entrainment. Regarding the first point, motor areas showed clear delta phase entrainment in both controls and PD patients (**chapter 4**). With respect to the second form of predictions, the response times in **chapter 4** showed that both groups could process the information value of the standard tones and speed their responses according to target-likelihood. These behavioural findings were accompanied by an increase in motor cortex delta phase entrainment, that increased with target likelihood (see Figure 6.1C). The fact that PD patients show normal behaviour and modulations of oscillatory activity, might be due the explicit instructions about the relation between

standard tones and target likelihood. Such an effect would be in line with earlier results (Cunnington et al., 1999), showing that PD patients show normal movement preparatory EEG activity when specific task-properties are explicitly pointed out to them. The explicit instructions about target likelihood might also be an explanation of why there was reduced delta phase entrainment in PD patients compared to controls in **chapters 2 and 3**, but no difference between groups in **chapter 4**. However, while PD patients did show a normal modulation of response times and neural activity by target likelihood, the ERF after tone omissions did show a reduced or absent omission response in patients over central-parietal areas (**chapter 4**). This reduced activation of centro-parietal areas in patients could reflect a deficit in the centro-parietal anticipatory network, which is important in translating sensory information into operative motor commands (Babiloni et al., 2006; Fogassi and Luppino, 2005).

In addition to unimodal effects, there are also cross-modal entrainment effects, as numerous studies have shown that primary sensory cortices are not the exclusive domain of a single sense (Bizley et al., 2007; Escoffier et al., 2010, 2015; Miller et al., 2013a; Schroeder et al., 2001; ten Oever et al., 2014). Anatomically, there are direct connections between auditory and visual cortices (Falchier et al., 2002) and between auditory and somatosensory cortices (Cappe and Barone, 2005), and physiologically it has been shown that somatosensory stimuli can lead to a phase reset in auditory cortex (Lakatos et al., 2007). This points to the fact that, besides stimuli of the preferred modality, ongoing activity can be modulated by cross-modal inputs related to non-preferred modality stimuli (Escoffier et al., 2015; Lakatos et al., 2007, 2008). A similar process holds for sensory information influencing ongoing activity in the motor cortex, as visual (**chapters 2, 3 and 5**) and auditory (**chapters 4 and 5**) information modulates motor delta oscillations. However, not all sensory input can reset ongoing neuronal oscillations and a solution was proposed in the form of a 'leading sense', which determines at a supramodal level which sensory inputs can modulate ongoing activity (Lakatos et al., 2009). The modality of the leading sense is dynamic and determined based on stimulus salience and attention (Lakatos et al., 2009). This hypothesis is supported by the finding that, in contrast to ignored stimuli, attended stimuli in one sensory modality can affect processing of inputs in another modality (Busse et al., 2005; Lakatos et al., 2009; Talsma et al., 2007). This process was of main interest in **chapter 5**, where subjects had to respond to deviant stimuli in a rhythmic stream of auditory or visual stimuli. However, the auditory and visual stimuli were presented either in isolation (only auditory or visual), or simultaneously but in anti-phase and subjects only attended one modality. The latter, bimodal, conditions put a greater demand on internal attentional control, as subjects have to generate and maintain an attentional set for the relevant modality (the 'leading sense'). Studies on attention in PD typically show that patients are particularly impaired in this internal or top-down attentional control (Cools et al., 2009; Tommasi et al., 2015). While the overall behavioural results in **chapter 5** (detection rate and response time) did not differ between groups, there was significantly reduced motor entrainment in PD patients as indexed by beta power modulations.

Entrainment of beta oscillations

While the previous section is mainly focussed on the (phase) entrainment of slow delta oscillations, also the power of faster beta oscillations shows entrainment to the task rhythm. Given the important role of beta oscillations in movement, auditory-motor interactions and rhythm processing, the current section is devoted to beta oscillations.

The motor system is not only involved in movement, but also has an important role in perception (MacEvoy et al., 2009; Martinez-Conde et al., 2008). The suggestion has been made that perception can be seen as an 'active sensing' process, since most of the sensory input to the brain is due to motor actions, and this has consequences for sensory processing (Schroeder et al., 2010). Accordingly, it has been suggested that the motor system is at the top of the cortical hierarchy involved in the perception-action cycle (Fuster, 1990; Morillon and Schroeder, 2015), might be responsible for the attentional allocation required at a supramodal level for the 'leading sense' (Lakatos et al., 2009), and that the motor system can be regarded as a predictive system that generates top-down (temporal) predictions that shape perception (Arnal and Giraud, 2012; Grahn and Rowe, 2013; Schroeder et al., 2010; Schubotz, 2007). These top-down temporal predictions are important, as accurate predictions about when something will happen optimizes the allocation of attentional resources in time, thereby facilitating sensory processing and speeding up behavioural responses (Correa et al., 2005; Nobre et al., 2012). Recent studies have shown that the motor system indeed plays a key role in timing and time perception (for reviews see Coull et al., 2011; Matell and Meck, 2004; Merchant et al., 2013). Moreover, studies on beat and rhythm perception have consistently shown involvement of the motor system (Grahn and Rowe, 2009, 2013; Teki et al., 2011; Zatorre et al., 2007). The predominant oscillatory rhythm in the motor system are beta-band oscillations, and given the evidence that the motor system is involved in temporal predictions, suggestions have been made that these predictions are sent through beta-band oscillations (Arnal, 2012; Fujioka et al., 2009, 2012; Teki, 2014). Therefore, the prominent role of beta oscillations in **all chapters** of this thesis was not without reason.

While beta oscillations were already extensively introduced in section 1.3 of the Introduction, it is worth mentioning again that beta-band oscillations are not only modulated during movement, but also undergo changes in anticipation of a movement, reflecting anticipatory processes (Alegre et al., 2003; Androulidakis et al., 2007a; Donner et al., 2009). Moreover, complementary to delta phase entrainment, the predictive nature of beta power changes plays an important role in temporal attention (van Ede et al., 2011). This finding lends support to the notion that beta power modulations have a general role during anticipatory processing and that beta-band oscillations signal the tendency of the sensorimotor system to maintain or change the current motor set (Engel and Fries, 2010; Jenkinson and Brown, 2011). Since beta oscillations signal the likelihood for a new upcoming response, this implies that beta-band oscillations have an important role in at least some forms of top-down predictions (Arnal and Giraud, 2012; Michalareas et al., 2016), which agrees with beta power being predictively suppressed by temporal

predictions (**all chapters**), effector predictions (**chapter 2**) and predictions on target-likelihood (**chapter 3**). In all chapters of this thesis, I have investigated beta power changes in terms of two variables named the beta modulation depth and the predictive beta modulation. These two variables are complementary to each other and each important in its own way. While the beta modulation depth describes the maximal change in beta power over time, the predictive beta modulation describes the amount of anticipatory power change. In terms of aforementioned theories, the beta modulation depth gives clues on the strength of predictions and accompanying flexible behavioural control, while the predictive beta modulation gives information on the temporal component of these predictions and anticipatory processing.

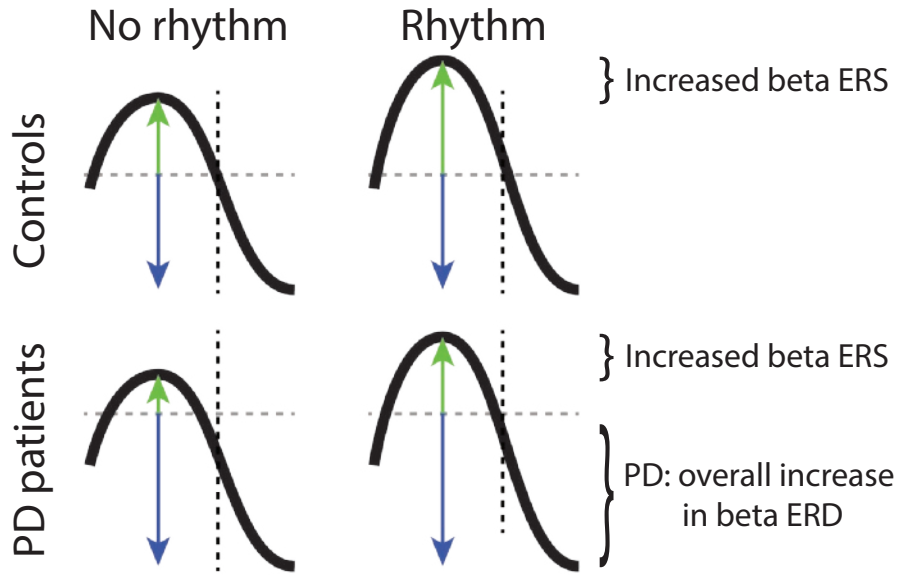

Figure 6.2 Schematic overview of beta power changes in terms of the beta modulation depth (full size of arrow) and the predictive beta modulation (green part of arrow), in controls (top) and PD patients (bottom) during non-rhythmic (left) and rhythmic (right) stimulus presentation. In both healthy subjects and PD patients, rhythmic stimulus presentation increases the beta modulation depth by an increase in the ERS phase only, thereby increasing the predictive beta modulation as shown in chapter 3. This is suggested to reflect an increased reliance on internal, feedforward predictions. Note that PD patients show an overall increase in beta ERD, possibly reflecting deficient rhythm generation mechanisms and increased reliance on external cues.

An increased modulation depth would point to stronger predictions and a greater predicted need for action, with more certainty about when the action should be performed. With respect to this last point, an increased beta modulation depth causes a stronger segregation between states of high (ERD) and low (ERS) action readiness. Results showed that, indeed, the beta modulation depth increased

when stimulus timing was more predictable, as in rhythmic versus non-rhythmic stimulation (**chapter 3**; see Figure 6.2). Note that this increased modulation depth or entrainment of beta power has a lot of resemblance with the entrainment of delta oscillations in rhythmic environments and the creation of 'attentional windows' (Schroeder and Lakatos, 2009). The reduction of beta power before stimulus onset in **all chapters** supports the suggestion that the changes in beta power reflect a predictive adjustment of cortical excitability (Lakatos et al., 2013b). However, the modulation depth is not only used to determine motor readiness in time, but also across hemispheres as the modulation depth was larger in the hemisphere contralateral to the response hand (**chapters 2 and 3**), with the hemispheric difference being larger with stronger effector predictions (**chapter 2**; Doyle et al., 2005b). The task-relevance of beta power modulations was underscored by results of **chapter 4**, where I showed that these power modulations only occur over task-relevant neural areas. Regarding the beta modulation depth, one has to keep in mind that there are multiple anticipatory and reactive processes happening simultaneously that all have an effect on beta power changes (for review see Kilavik et al., 2013). Since the beta modulation depth is simply defined as the difference between maximal ERS and ERD, a summation might be made over multiple processes. This could be an explanation of why there was no difference in beta modulation depth between healthy controls and PD patients in **chapters 2 and 3**, while a difference between groups was found in **chapters 4 and 5**. Namely, reduced anticipatory processing in patients is compensated for by increased reactive processing. As all stimuli in **chapters 2 and 3** required a response, there always was a reactive beta power change that increased the modulation depth in patients. On the other hand, the experiments in **chapters 4 and 5** only required a response after targets and there was no reactive beta power change needed after non-target stimuli, hence the reduced modulation depth in patients. This last point illustrates the need for a variable that describes beta power changes in the temporal domain (the predictive beta modulation), as the modulation depth was not able to capture the reduced anticipatory processing of PD patients in **chapters 2 and 3**. The predictive beta modulation describes the size of anticipatory power changes with respect to the modulation depth. The predictive part increases with stronger predictions about stimulus timing (**chapter 3**), and the effector to be used (**chapter 2**). Moreover, the predictive beta modulation was able to perfectly capture the deficient anticipatory processing in PD patients compared to controls, with its behavioural relevance underscored by the correlation with response time (**chapters 2 and 3**).

An important open issue was whether the reduced entrainment of beta oscillations, as found in **chapters 2 and 3**, occurred only over motor areas or whether this is a general phenomenon in PD patients. In **chapters 4 and 5**, I found that the reduced entrainment was confined to motor areas only, suggesting a deficit in PD patients in translating sensory entrainment to motor circuits, most likely due to disease-related changes in the motor system. The deficient motor entrainment in PD patients was not resolved by increasing the benefit of entrainment, by means of addition of a stream with distractor stimuli, as shown in **chapter 5**. These results also showed that entrainment leads to motor readiness at the predicted time of stimulus presentation, as the entrainment strength was correlated with hit rate of

deviant stimuli. Interestingly, this correlation was only found in healthy controls and not in PD patients (**chapter 5**). While the results of **chapters 2, 3 and 4** already showed that the motor cortex is actively predicting and tracking the stimulus rhythm, this was strengthened by the results of **chapter 5**. Namely, in the bimodal conditions where two stimulus streams were presented simultaneously but in anti-phase, the motor cortex beta power modulations were also in anti-phase, showing only entrainment to the attended stimulus stream. At least, this was what was found in healthy controls, since PD patients showed no difference between attentional conditions (**chapter 5**), indicating impaired tracking and prediction of the attended rhythm in motor areas of PD patients.

In addition to the entrainment of beta oscillations by the isochronous stimulus presentation in **chapter 4**, I also investigated the beta power modulations by means of more explicit and discrete predictions. Namely, on top of the temporal predictions, subjects also formed more discrete predictions about target likelihood on a trial-to-trial basis. The prediction of targets was also more explicit in the sense that subjects were instructed about the relation between the pitch of standard tones and target likelihood, while I did not instruct subjects about the temporal predictability. In addition to the reduced anticipatory processing of temporal information in PD patients shown in **chapters 2, 3 and 4**, also the results of these more discrete predictions showed deficient anticipatory processing in patients. Standard tones induced more beta ERD over motor areas in controls than in PD patients. The fact that this beta ERD reflects anticipatory processing is supported by the stronger beta ERS after tone omissions in controls compared to patients, with the ERS reflecting movement suppression (Androulidakis et al., 2007a). This relation between amount of pre-omission preparation and post-omission suppression was underscored by the correlation between beta ERD and ERS (**chapter 4**). However, while overall anticipatory processing was reduced, patients could still make use of the predictive value of the standard tones, as shown by the faster response times with stronger predicted targets and by the modulation of beta ERD by target likelihood in both controls and patients. In addition, tones that were more predictive of an upcoming target induced stronger beta ERS when that target was omitted (**chapter 4**). These results are in line with earlier work showing that the more a cue is predictive of a required movement, the stronger beta power is suppressed (Tzagarakis et al., 2010), not only in healthy subjects but also in PD patients on and off medication (Williams et al., 2003), and with work showing that PD patients can exploit advance information if it is more explicit (Cunnington et al., 1999; Praamstra et al., 1996b). Moreover, the results also agree with the findings in **chapter 2 and 3**, showing an overall reduction in anticipatory processing in PD patients but still a modulation by effector (**chapter 2**) and temporal predictability (**chapter 3**).

Cross-frequency coupling and attentional processing

While I have only focussed on oscillations of a single frequency-band in the previous sections, natural stimuli might have information on multiple temporal scales. To optimize processing of such stimuli, oscillatory activity needs to simultaneously entrain at multiple frequencies, and such a dynamical structure is exactly what has

been found (Gomez-Ramirez et al., 2011; Henry et al., 2014). Moreover, while the oscillatory selection hypothesis mainly refers to slow oscillations in the delta and theta frequency ranges, also faster oscillations in the alpha and beta bands play a functional role during temporal expectations and attention (Large, 2008). The low frequency oscillations are thought to modulate activity over large spatial regions in long temporal windows, whereas faster oscillations modulate activity in smaller spatial regions and in shorter temporal windows (VanRullen and Koch, 2003; Von Stein and Sarnthein, 2000). Several studies have shown that the information in these different frequency-bands can be integrated by means of a hierarchical structure in oscillatory activity (Lakatos et al., 2005; Palva et al., 2005). Namely, studies have shown a statistical relationship (cross-frequency coupling) between the phase of slow oscillatory activity and the amplitude or power of higher frequency activity (for reviews see Canolty and Knight, 2010; Jensen and Colgin, 2007). This means that, for example in the context of rhythmic stimuli, the entrainment of slow oscillations causes periods of high gamma power to align with the onset of external stimuli, thereby facilitating their processing (Lakatos et al., 2008).

Relevant for this thesis, it was shown that during rhythmic stimuli, delta phase and beta power in motor areas entrain to the rhythm of stimulus presentation and work together to enhance sensitivity to attended, predictable, and task-relevant cues (Saleh et al., 2010), and that the behavioural outcome depends on the accuracy with which the coupling is implemented (Arnal et al., 2015). This suggests that cross-frequency interactions are dynamically implemented and used to optimize neural processing at particular moments in time, in specific neural regions, or used to couple cortical and subcortical areas during motor behaviour (von Nicolai et al., 2014). Similar results have been found for the coupling between theta phase and beta power, and were suggested to reflect a central mechanism for controlling neural excitability according to temporal expectations (Cravo et al., 2011). Interestingly, many studies have shown that PD affects the contingent negative variation (CNV) (Cunnington et al., 1995; Ikeda et al., 1997; Praamstra and Pope, 2007), and the suggestion has been made that the CNV is actually a reflection of entrained delta oscillations (Lakatos et al., 2008). Given the coupling between delta and beta oscillations, it is tempting to relate the reduced CNV amplitude to the deficient beta power entrainment in PD patients shown in **all chapters** of this thesis. The correlational evidence for a coupling between predictive beta modulation and delta phase entrainment, as presented in **chapters 2 and 3**, would fit the aforementioned suggestion. The temporal predictability of the stimuli leads to entrainment of delta phase and beta power in motor areas, with their coupling optimizing sensitivity to respond to external stimuli (Saleh et al., 2010). The dynamic implementation of this coupling between delta phase and beta power was shown in the modulation by effector predictability (**chapter 2**), and by temporal predictability (**chapter 3**). Regarding the latter, when temporal predictability is high, such as during rhythmic stimulus presentation, delta phase and beta power can entrain to the stimuli and work together to optimize processing of those stimuli. On the other hand, when stimulus timing is unpredictable the system suppresses slow oscillations and tries to operate in a more continuous mode of attention. This is reflected in the absence of a correlation between delta phase and beta power during the non-rhythmic

stimulation condition in **chapter 3**, possibly to maintain a higher state of motor readiness throughout time.

While we did mention the close resemblance between beta and gamma power time courses in **chapter 2**, suggestive of some sort of hierarchical coupling, there was no difference between groups regarding this relation between beta and gamma. However, there is work showing an aberrant coupling between beta phase and gamma power in PD patients (de Hemptinne et al., 2013; Yang et al., 2014). This abnormally strong coupling is suggested to allow only a monotonous pattern of coupling, causing the neural tissue to be less able to dynamically respond to external signals, representing a possible basis for akinesia in PD.

6.3 Neurophysiology of cueing in PD

In this section I will discuss the neurophysiology of rhythmic cueing in PD. First, I will briefly summarize current ideas about the physiology of cueing. The remainder of the section is devoted to the presentation of recent insights that challenge these ideas, and the integration of these new insights with the findings of this thesis into a framework that can explain the behavioural effects seen during rhythmic cueing.

Most studies on rhythmic cueing state that external cues facilitate movement because they recruit lateral premotor areas and make use of cerebellar-thalamocortical circuits, thereby bypassing basal ganglia-medial premotor circuits that are affected in PD (Benoit et al., 2014; Cunnington et al., 1995, 2001; Rochester et al., 2007; Vercruysse et al., 2012; Yu et al., 2007). This notion of the physiology of cueing can be broadly summarized as involving a shift in activation from medial to lateral premotor cortex and, subcortically, a shift from processing in the basal ganglia to the cerebellum (Hughes et al., 2010). Cueing would thus activate pathways that are important in processing reactive or externally driven movements, and would not be processed by (deficient) pathways that play an important role in processing anticipatory or self-generated movements. Building on these ideas, it has been suggested that cueing approaches in PD are mainly effective because they strengthen compensatory pathways that exclude the basal ganglia (Nombela et al., 2013). However, recent work (see section 1.1 of the Introduction in this thesis) and findings in this thesis have challenged this view on the physiology of cueing; I will present a different perspective on the neurophysiology of cueing in the following section.

A new perspective on the neurophysiology of cueing

The evidence that rhythmic cueing improves motor function in PD patients is considerable (for reviews see Lim et al., 2005; Spaulding et al., 2013; section 1.1 of the Introduction of this thesis). Against the background presented in the previous sections and results of **all chapters** in the current thesis, I propose the following mechanism.

The rhythmic external cues affect oscillatory activity in sensory areas and lead to a bottom-up entrainment of neural oscillations in those areas. In addition, the rhythm

represented in these cues is detected and sustained (internally generated) by the cortico-striatal network (Kotz et al., 2016), to form active temporal predictions in order to anticipate upcoming stimuli. These temporal predictions are transferred to motor and back to sensory areas (top-down entrainment) to optimize processing of predicted upcoming stimuli (Morillon et al., 2014). This optimization might be instantiated by aligning the phase of delta oscillations with the onset of the external stimuli, hence through entrainment. Such a process can explain the finding that entrainment occurs in a network involving the primary sensory cortices and motor areas (Besle et al., 2011; **chapter 4**), which has considerable overlap with the network involved in 'attention to time' (Coull and Nobre, 1998; Nobre et al., 2007). Additionally, the optimization of motor areas for future movements is also signalled by the power of beta oscillations, as the amount of (predictive) beta suppression signals motor readiness (Engel and Fries, 2010; Jenkinson and Brown, 2011).

The process of bringing motor areas into an optimal state in order to respond to external stimuli was specifically tested in **chapter 3**, where I showed that rhythmic stimuli could facilitate movement by both an increase in delta phase entrainment and an increased beta modulation depth, which is typically reduced in PD (Degardin et al., 2009; Devos et al., 2003; Doyle et al., 2005a; Heinrichs-Graham et al., 2013; **chapters 4 and 5**). This increase in beta modulation depth was solely caused by an increase in the ERS phase of the beta power cycle, thereby increasing the predictive beta modulation (see Figure 6.2). The increased beta ERS, with similar spatial distribution in both groups, is in agreement with the predictive nature of basal ganglia involvement in rhythm processing. That is, as already mentioned in **chapter 3**, the amplitude of the beta ERS is thought to be related to the updating of an internal model (Tan et al., 2014a). High amplitude beta ERS functions to preserve the current set of motor commands, whereas lower amplitude beta ERS allows for updating of the motor set (Brittain and Brown, 2014; Engel and Fries, 2010). This provides a conceptual link between beta ERS amplitude, predictive beta modulation and the preparation for an upcoming movement. Interestingly, recent work refines the above hypothesis on the relation between beta ERS amplitude and updating of the internal model. Using an out-and-back aiming task, it was shown that the beta ERS amplitude is negatively correlated with the estimation uncertainty associated

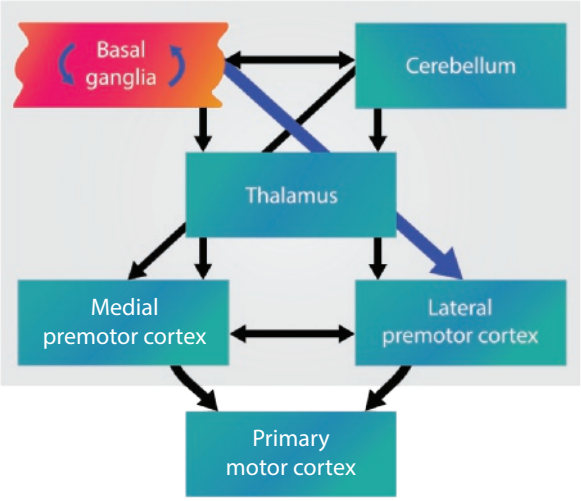

Figure 6.3 Schematic overview of the neurophysiology of cueing based on findings in this thesis and recent research. While the cerebellum and lateral premotor cortex are still important during cueing, the rhythm of the cues is detected and internally generated by the basal ganglia. This leads to a predictive mode of processing, as shown by an increased beta modulation depth and predictive beta modulation over the primary motor cortex. In short, cueing in PD works because of a facilitation of processing in the basal ganglia and lateral premotor cortex (blue arrows).

with feedforward predictions of the internal model (Tan et al., 2016). Now, when stimulus timing becomes more predictable, as in rhythmic cueing, the uncertainty in the temporal aspects of the feedforward predictions is reduced, causing the motor system to rely more on the feedforward predictions than on sensory feedback (Tan et al., 2016). This increased reliance on feedforward predictions agrees with the increase in predictive beta modulation as shown in **chapters 2 and 3**. Since temporal predictions are, at least partly, generated by the basal ganglia (putamen) (Grahn and Rowe, 2013), the increased beta ERS and subsequent increased predictive beta modulation are suggested to reflect increased basal ganglia processing during rhythmic cueing (see Figure 6.3). Importantly, since I used both visual (**chapters 2, 3 and 5**) and auditory (**chapters 4 and 5**) stimuli, the role of the basal ganglia in rhythm perception is supramodal (Araneda et al., 2017). In the proposed view, rhythmic cueing does not bypass the basal ganglia (substituting a reactive for a predictive mode of control), but instead supports processing in the basal ganglia and lateral premotor cortex, which is of a predictive nature (Grahn and Rowe, 2013). This is supported by the sensory gating effect shown in **chapter 3**, which was a strong confirmation that both controls and PD patients deployed a predictive mode of cue utilisation.

During this process, the cerebellum might play a role in detecting timing errors between temporal predictions and actual stimulus presentation, allowing slight adjustments to optimize synchronization (Bijsterbosch et al., 2011; Jueptner and Weiller, 1998). Remember that this process of reactive error correction is important for accurate entrainment (Repp and Keller, 2008; Repp and Su, 2013; section 1.2 of the Introduction of this thesis). The fact that there is simultaneous processing in the beat-based and duration-based timing network (including the cerebellum) is an explanation of why both controls and PD patients showed similar responses to deviant time intervals in **chapter 2**. This in line with earlier findings of deficient temporal preparation for voluntary, but not for reflexive behaviour in PD patients, with the latter largely based on duration-based timing in the cerebellum (Jurkowski et al., 2005; Praamstra and Pope, 2007).

Since PD patients suffer from impaired basal ganglia function and subsequently show deficient internal rhythm generation (reflected by the reduction in predictive beta modulation as shown in **chapters 2 and 3**, and the reduced beta modulation depth in **chapters 4 and 5**), the oscillatory entrainment over motor areas is reduced in PD patients. Rhythmic stimulation or cueing, however, might not only assist with the initiation phase of movement as a replacement of the deficient starting signal in PD, but also facilitate movement once the movement has started. That is, the rhythmic stimuli lead to enhanced activity in the basal ganglia-cortical circuit (Kotz et al., 2016). The results of **chapter 3** support this idea of increased basal ganglia activity during rhythmic stimuli, even in PD patients (**chapter 3**). This suggests, contrary to the common view on cueing discussed above, that rhythmic cueing facilitates processing in the basal ganglia-premotor cortex circuit, rather than bypassing it. The facilitation of processing in this circuit is likely to improve internal rhythm generation, which leads to an increased beta modulation depth (**chapter 3**). This increased modulation depth might benefit movement, as it increases the typically reduced physiological range of beta power changes in PD patients

(Jenkinson and Brown, 2011). Since entrained oscillations can outlast the external stimulation (Lakatos et al., 2013a; Spaak et al., 2014), this might be an explanation of the finding that positive effects of cueing can still be seen (albeit briefly) after presentation of the cues has stopped (McIntosh et al., 1998; Nieuwboer et al., 2007). Note however, that while rhythmic stimulation produces the same benefits in controls and PD patients, there was an overall reduction in predictive motor activation in patients. Since predictions are also sent back to sensory areas (Morillon et al., 2014), it seems odd that PD patients did show 'intact' entrainment over sensory areas, as shown in **chapters 4 and 5**. An explanation for this finding might be that this entrainment is more of the bottom-up or stimulus-driven type, and that these bottom-up effects are stronger than any top-down modulations (Lakatos et al., 2005). That is, while sensory cortices are under the influence of both bottom-up and top-down entrainment, the motor areas are only generating top-down entrainment. In fact, some researchers have even suggested that the term 'motor system' would better be labelled as the 'prediction system' (Schubotz, 2007).

In sum, the generally accepted view of a strong distinction between internally generated and externally cued movements, being generated by the medial and lateral premotor cortices respectively, and supported by the basal ganglia and the cerebellum subcortically, does not seem plausible in light of the findings presented in this thesis. There appears to be, at the very least, some overlap in the network responsible for processing internally generated and externally cued movements. Such a conclusion is in line with the finding that the network used in externally cued movements can benefit from internally generated movements, suggesting that there might even be one single motor (preparatory) system underlying both types of movements (Hughes et al., 2011).

6.4 Limitations

Effect of dopaminergic medication

It is important to mention that all PD patients that participated in the experiments described in this thesis were using dopaminergic medication. While all PD patients were tested in the OFF-state (>12h withdrawal of medication, i.e. a so-called practically defined off state), some issues are worth addressing at this point. First, the 12-hour period of medication withdrawal is probably much too short to eliminate all influences of dopaminergic medication. When testing PD patients that have withdrawn their medication for a much longer time period, the between-group effects are probably much larger than described in the previous chapters. Second, it has to be noted that the between-group differences are most likely smaller when patients are ON medication. In such conditions, the dopamine levels of PD patients are more similar to those in healthy subjects, with consequently more similar results in beta power changes (Jenkinson and Brown, 2011). Third, in **chapter 3**, the suggestion was made that rhythmic stimuli might improve movement by facilitating processing along basal ganglia-cortical circuits, leading to enhanced internal rhythm generation, which might be particularly beneficial in PD patients. As these results were already visible in patients during the OFF-state, the beneficial effects

are probably even larger in the ON-state, as dopaminergic medication has been shown to increase reactivity of beta power (Oswal et al., 2012).

Implicit versus explicit task-instructions

All studies in this thesis were performed with implicit task-instructions regarding the temporal predictability of the stimuli. A general finding throughout all experiments was that PD patients did not show a predictive processing mode. This suggests that patients cannot make use of the implicit temporal predictability, inherent in the rhythmic stimuli. This difference between healthy controls and patients might be reduced by explicitly instructing patients to make use of the temporal predictability of the cues, as studies have shown that PD patients only show a predictive processing mode when explicitly instructed to attend to the temporal properties of the task (Cunnington et al., 1999). Results of **chapter 4** support this idea, as PD patients could make use of the target likelihood signalled by the pitch of standard tones, a relation about which they were explicitly instructed about just before the experiment.

Translating results from hand to leg movements

While aforementioned studies on entrainment and rhythmic cueing all report positive effects on gait, it is important to mention that several studies have shown similar effects for arm and hand movements (Vercruysse et al., 2012). These findings are important with respect to the results in this thesis, as I have used hand movements in **all chapters**, and it is crucial to know whether the results of these studies can be translated to the lower extremities in order to draw conclusions about the physiology of cueing during gait rehabilitation. Importantly, in a study that was much like the work presented in **chapter 2** and a study by Praamstra and Pope (2007), it was shown that entrainment of leg movements has the same neurophysiological correlates as hand movements (Heideman et al., 2015). Moreover, it has been shown that finger and foot tapping are strongly correlated with respect to the underlying timing mechanisms (Keele et al., 1985). Neuroimaging work has shown similar activations for upper and lower limb movements in a network involving primary motor and sensory cortex, SMA, basal ganglia and the cerebellum, with little differences due to the somatotopic organization of these areas (Sahyoun et al., 2004). However, other work has shown differences between upper and lower limb movements such as in neuronal activation (Lee et al., 2013), and in network connectivity and lateralization (Volz et al., 2015). In sum, while there seems to be much overlap between upper and lower limb movements in terms of cueing effects, timing mechanisms and neurophysiology, there should be at least some caution in translating the results of this thesis from hand to leg movements.

Stimulus timing and modality

A limitation of **chapters 2 and 3** is that we used visual stimuli only, at a presentation rate slightly slower than optimal for inducing entrainment. While there is rhythm perception in the visual domain, the sense of beat can be strengthened by

presenting several auditory stimuli in advance of the visual stimuli (Grahn et al., 2011). Studies on rhythm perception have shown that the beat is best perceived when the pace is below 5 Hz (Nozaradan et al., 2017; Van Noorden and Moelants, 1999), with subsequent positive effects for sensorimotor synchronization (Repp, 2005) as many rhythmic actions have this time scale. Other work has shown that rhythm perception is optimal when stimuli are presented at intervals of 500 ms and that in this range the largest deficits in PD patients are seen, but not at 1 or 1.5s (Miller et al., 2013b). However, with stimulus modality and frequency optimised to induce strong entrainment, the observed predictive mode of cue utilisation (**chapter 3**) is more likely to be strengthened than to be reversed. This was indeed the case in **chapters 4 and 5**, where we found similar effects but using auditory (and visual) stimuli at a slightly faster stimulation rate.

6.5 Conclusion

The research reported in this thesis does not yet provide a full picture of the neurophysiology of cueing in PD. One might even say it yielded findings that are not easy to reconcile. On the one hand, a direct comparison between rhythmic and non-rhythmic stimulation showed similar effects of rhythmic stimulation for healthy controls and PD patients. The similar enhancement of the beta-ERS phase, with consequent increase of a prospective beta power modulation, points to a predictive mode of cue utilisation in both patients and control subjects. This predictive mode of cue utilisation is an argument for cueing being dependent on, and promoting basal ganglia-cortical interactions. This view contrasts with the popular view of cues conferring a special advantage based on recruitment of alternative pathways.

On the other hand, not all the findings fit easily into this picture. In the experiments where participants made serial motor responses to series of stimuli, the modulation depth of motor cortex activity was the same in patients and controls, but the pattern was more reactive in patients, with more reactive than prospective beta-ERD. Likewise, when attentively tracking stimulus series for occasional targets to respond to, patients showed very little entrainment of motor cortical activity, while healthy controls demonstrated fluctuations in motor readiness entrained by the stimulus rhythm. Hence, in patients the external stimulation failed to engender an internal rhythm modulating response readiness.

In spite of the fact that the findings do not converge to support a single and simple explanation of the clinical benefit of rhythmic cueing in PD, the research supports the value of neurophysiological analyses of oscillatory activity to describe the neurological basis of entrainment. Conversely, the study of rhythmic cueing in PD, the effects of which presumably depend on entrainment, has proven a productive testing ground for neurophysiological theories emphasizing an important role of oscillatory entrainment in cognitive and motor behaviour.

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Nederlandse samenvatting

De ziekte van Parkinson is één van de meest voorkomende neurodegeneratieve aandoeningen in Nederland en is de belangrijkste oorzaak van bewegingsstoornissen. De nadelige gevolgen van Parkinson op het motorisch functioneren worden vooral duidelijk bij het lopen. Patiënten lopen vaak met een hoog tempo en zetten kleine, onregelmatige stappen. De grote variabiliteit in stapgrootte kan er soms toe leiden dat patiënten 'bevriezen' en ze letterlijk geen stap meer kunnen zetten; ze hebben het gevoel dat hun voeten vastgelijmd zitten aan de grond. Het onregelmatige looppatroon en het bevriezen leiden ertoe dat patiënten vaker vallen, met zeer nadelige gevolgen voor hun kwaliteit van leven en levensverwachting. Gelukkig kunnen veel motorische symptomen van de ziekte van Parkinson (tijdelijk) worden verholpen met medicatie, maar loopproblemen vallen hier niet onder. Het kleine effect van medicatie op loopproblemen, wat ook nog eens afneemt over tijd aangezien Parkinson een progressieve ziekte is, heeft ervoor gezorgd dat er werd gezocht naar alternatieven om deze loopproblemen te verbeteren. In de fysiotherapie is het bekend dat het aanbieden van ritmische stimuli, ook wel "cueing" genoemd, het lopen van Parkinson patiënten kan bevorderen. Studies, soms met meer dan 150 patiënten, hebben inderdaad laten zien dat patiënten baat hebben bij cueing en dat patiënten niet alleen makkelijker kunnen beginnen met lopen, maar dat de cues tijdens het lopen ook zorgen voor grotere stappen, een stabieler ritme, een betere balans en minder bevriezen.

Er wordt gedacht dat de positieve effecten van cueing worden veroorzaakt door het feit dat de ziekte van Parkinson met name hersengebieden aantast die belangrijk zijn voor vrijwillige of zelfgeïnitieerde bewegingen (zoals het zelfstandig lopen), terwijl hersengebieden die belangrijk zijn voor reactieve bewegingen juist gespaard blijven (zoals het zetten van een stap in reactie op een externe stimulus). Deze visie op cueing claimt dat de externe ritmische cues beweging mogelijk maken omdat deze zorgen voor activatie van de laterale premotor cortex, terwijl zelfgeïnitieerde bewegingen juist worden voorbereid in de mediale premotor cortex. Daarbij wordt gedacht dat de mediale premotor cortex, in tegenstelling tot de laterale, zijn signalen ontvangt van de basale ganglia. Aangezien de ziekte van Parkinson vooral de functie van de basale ganglia aantast, heeft dit effect op signaalverwerking in de mediale premotor cortex en daardoor vooral op zelfgeïnitieerde bewegingen. Reactieve bewegingen worden in deze theorie dus niet door de basale ganglia en mediale premotor cortex verwerkt en blijven dus intact. Dit vormt de basis voor het gebruik van cueing in revalidatie. Echter, deze visie op de neurofysiologie van cueing is achterhaald, aangezien onderzoek heeft aangetoond dat de basale ganglia ook verbonden zijn met de laterale premotor cortex en dat de basale ganglia niet alleen een rol spelen in zelfgeïnitieerde, maar ook in reactieve bewegingen. Daarnaast tonen neurowetenschappelijke onderzoeken aan dat er geen sterke scheiding is van hersengebieden die belangrijk zijn bij zelfgeïnitieerde en reactieve bewegingen.

De onduidelijkheid over de neurofysiologie van cueing neemt niet weg dat cueing werkt. Echter, er is ook groeiend bewijs dat Parkinson patiënten niet gevoelig zijn voor regelmatige omgevingspatronen en zelfs moeite hebben om regelmaat waar te nemen, hoewel dit een voorwaarde lijkt voor het gebruik van cueing. Daarnaast laat

onderzoek bij gezonde personen zien dat hun hersengolven synchroniseren met externe ritmische stimuli, terwijl patiënten deze synchronisatie niet laten zien. Deze ongevoeligheid van patiënten voor externe ritmes kan mogelijk verklaren waarom de effecten van cueing vaak niet meer, of sterk verminderd te zien zijn nadat de cues gestopt zijn. Als patiënten inderdaad niet het ritme 'voelen', dan heeft dit grote gevolgen voor het gebruik en de ontwikkeling van cueing toepassingen bij de revalidatie van deze patiënten. In dit proefschrift probeer ik een verklaring te vinden voor deze ontstane paradox: patiënten kunnen dus moeilijk ritmes waarnemen, maar gaan er wel beter van lopen. Dat doe ik enerzijds om de functie van de basale ganglia beter in kaart te brengen, anderzijds om de neurofysiologie van cueing te bepalen en zo mogelijk toekomstige revalidatiemethoden te verbeteren.

Ik onderzoek de neurofysiologie van cueing met behulp van met magneto-encephalografie (MEG) geregistreerde hersengolven. Er wordt gedacht dat deze hersengolven de prikkelbaarheid van het onderliggende neurale weefsel weergeven. Op de piek van de golf is de prikkelbaarheid hoog en worden signalen snel verwerkt (ideale fase), terwijl dit tijdens een dal precies omgekeerd is (slechte fase). Nu heeft onderzoek aangetoond dat trage hersengolven, maar ook de daaraan gekoppelde snellere hersengolven, synchroniseren met externe cues. Deze synchronisatie vormt mogelijk de basis van positieve cueing effecten, omdat de ideale fase van de hersengolven dan steeds samenvalt met de externe cue, wat zorgt voor verbeterde perceptie en motorische prestaties. Om dit te toetsen wordt in dit proefschrift deze tendens tot spontane synchronisatie vergeleken in patiënten en controles. In vier verschillende onderzoeken varieer ik steeds andere parameters (het ritme, de effector, de stimulusintensiteit, stimulusmodaliteit, etc.) om te zien wanneer synchronisatie wel en niet goed gaat bij patiënten. Naast de tendens tot synchronisatie zelf, is het belangrijk vast te stellen welke hersengebieden normaal en welke gebieden abnormale synchronisatie vertonen. Het kan namelijk best zijn dat patiënten überhaupt geen synchronisatie laten zien, of dat ze dit wel laten zien in sensorische gebieden maar niet in motorische gebieden. Uiteindelijk geeft deze aanpak inzicht in de mogelijkheden en beperkingen van cueing, en in de rol van hersengolven in de pathofysiologie van de ziekte van Parkinson.

Een belangrijke klasse van hersengolven zijn die van de beta frequentie (13-30 Hz), want deze spelen een grote rol in het motorische systeem en komen bij patiënten met de ziekte van Parkinson versterkt voor. Men kan grofweg stellen dat betagolven antikinetisch zijn; hoe sterker hun aanwezigheid, hoe minder bewegingen en vice versa. Er wordt dan ook gesuggereerd dat de abnormaal hoge sterkte van betagolven bij Parkinson een oorzaak kan zijn van bradykinesia en akinesia. Echter, de exacte rol van deze betagolven is nog niet bekend, maar er is steeds meer bewijs dat suggereert dat veranderingen in sterkte van deze betagolven een anticiperende of voorspellende rol hebben, in voorbereiding op toekomstige bewegingen. In **hoofdstuk 2** heb ik de relatie onderzocht tussen veranderingen in sterkte van betagolven en de synchronisatie van trage en snelle hersengolven aan een ritmische taak. In één conditie (de 'willekeurige conditie') werden de stimuli ritmisch aan de proefpersonen aangeboden, maar was de volgorde van stimuli die voor een rechter

of linker hand beweging instrueerden willekeurig. In deze conditie was dus alleen synchronisatie aan het ritme mogelijk (temporele synchronisatie). In een tweede conditie (de 'voorspelbare conditie') werden de stimuli ook ritmisch getoond, maar werd er steeds afwisselend om een reactie met de linker- en rechterhand gevraagd. Hierbij was dus temporele synchronisatie mogelijk, maar ook effector synchronisatie. De reactietijden waren gelijk voor gezonde proefpersonen en patiënten, bovendien konden beide groepen gebruikmaken van de voorspelbare effector in de voorspelbare conditie. Analyses van hun hersengolven lieten echter een verschillend beeld zien tussen beide groepen. Bij patiënten was de verandering in sterkte van betagolven voorafgaand aan elke stimulus veel kleiner dan bij gezonde proefpersonen, terwijl de verandering in sterkte van beta golven ná elke stimulus juist groter was bij patiënten. In aanvulling op deze verandering van een anticiperende naar een reactieve modulatie van betagolven bij patiënten, lieten zij ook een trend zien tot verminderde synchronisatie van trage delta golven en latere gamma synchronisatie dan gezonde proefpersonen. De delta fasesynchronisatie was bovendien gecorreleerd met de anticiperende sterkteverandering van betagolven, wat de relevantie ondersteund van hiërarchische koppeling tussen hersengolven van verschillende frequenties. De resultaten van dit onderzoek laten dus zien dat de hersengolven van patiënten niet alleen temporele maar ook effector synchronisatie kunnen ondergaan, maar dat dit veel minder sterk gebeurd dan bij gezonde proefpersonen en dat deze modulatie veel reactiever van aard is in patiënten.

Voor een goede temporele synchronisatie is het belangrijk om het ritme van de externe stimuli waar te nemen en de basale ganglia spelen een belangrijke rol bij dit proces van ritmeperceptie. Het is dan ook niet verwonderlijk dat onderzoek heeft laten zien dat patiënten met de ziekte van Parkinson minder goed zijn in het waarnemen van ritmes. Desondanks leiden ritmische cues tot diverse positieve effecten bij revalidatie van het lopen, wat leidt tot de vraag hoe ritmes het lopen kunnen ondersteunen. Deze vraag stond centraal in het onderzoek zoals beschreven in **hoofdstuk 3** van dit proefschrift. In dit onderzoek maakte ik gebruik van een keuze-responstaak met ofwel ritmische presentatie van stimuli (de 'ritmische conditie') of niet-ritmische stimuli (de 'niet-ritmische conditie'). De analyses waren gefocust op (i) de synchronisatie van trage hersengolven aan het ritme van de taak, (ii) de grootte van de verandering in sterkte van betagolven (modulatiediepte) en (iii) of een toename van deze modulatiediepte, door ritmische stimuli, van een anticiperende of reactieve aard is. De resultaten laten zien dat patiënten een zwakkere fasesynchronisatie van trage hersengolven hebben en een verschuiving van anticiperende naar reactieve verandering in sterkte van bewegingsgerelateerde betagolven, zoals ook aangetoond in **hoofdstuk 2**. Desondanks zorgde ritmische stimuluspresentatie voor een gelijke stijging van de beta modulatiediepte bij gezonde deelnemers en patiënten. Belangrijker was dat deze stijging van de modulatiediepte kwam door een toename van anticiperende, en niet reactieve, bewegingsgerelateerde beta suppressie. Het feit dat de ritmische cues leiden tot een voorspellende / anticiperende manier van signaalverwerking wijst op een versterking van interacties tussen de basale ganglia en de (pre)motor hersenschors, in tegenstelling tot de huidige veronderstelde neurofysiologie van cueing waarbij de gedachte is dat deze gebieden juist worden

omzeild en alternatieve circuits worden gebruikt.

Elektrofysiologische studies, waaronder de resultaten uit **hoofdstukken 2 en 3**, suggereren dat Parkinson patiënten minder neiging hebben om te synchroniseren met omgevingsritmes. In **hoofdstuk 4** heb ik onderzocht of deze verminderde synchronisatie een algemeen effect is of dat dit beperkt blijft tot verminderde synchronisatie in motorische gebieden terwijl de synchronisatie in sensorische gebieden wel intact is. Alle deelnemers aan het onderzoek (gezonde personen en Parkinson patiënten) moesten een knop indrukken wanneer zij een 'targetgeluid' hoorden in een ritmische reeks van standaardtonen. De toonhoogte van de standaardtonen gaf aan hoe groot de kans was dat de volgende toon een targetgeluid was. Daarnaast werd op sommige momenten het targetgeluid weggelaten waardoor ik de synchronisatie van hersengolven kon onderzoeken zonder "vervuiling" van effecten veroorzaakt door stimuluspresentatie. De reactietijden waren niet verschillend tussen beide groepen en beide groepen konden even goed gebruikmaken van de voorspellende waarde van de standaardtonen. Analyses van de betagolven lieten zien dat de synchronisatie aan de ritmische geluiden gelijk was voor beide groepen over sensorische (auditieve) hersengebieden. Echter, betagolven en stimulusgerelateerde magnetische velden lieten zien dat motorische gebieden van patiënten veel minder sterk meededen in het ritme dan bij gezonde mensen. Dit werd uitgedrukt in de modulatiediepte van betagolven, de reactie op weggelaten targetgeluiden en in een afwezig P300-effect over motorische gebieden bij patiënten. Deze resultaten tonen dus aan dat synchronisatie over sensorische gebieden gelijk is voor gezonde personen en patiënten, maar dat patiënten niet of verminderd in staat zijn om deze synchronisatie te vertalen naar synchronisatie in motorische gebieden. Ik stel hierbij dat de verminderde motorische activatie niet simpelweg een verminderde resonantie op externe ritmische stimuli is, maar een verminderde capaciteit om een intern ritme te genereren.

Neurale synchronisatie speelt een cruciale rol in perceptie en actie, vooral wanneer stimuli een zekere temporele regelmaat hebben. Daarnaast wordt ook gesuggereerd dat deze synchronisatie een neuraal proces is om een bepaalde stimulusstroom te selecteren en alleen deze stroom te verwerken, bijvoorbeeld in situaties wanneer er meerdere stimulusstromen door elkaar worden aangeboden. De studies uit **hoofdstukken 2, 3 en 4** hebben laten zien dat patiënten een verminderde neiging tot synchronisatie hebben. Echter, neurale synchronisatie in Parkinson patiënten is alleen getest in paradigma's met een enkele stimulusstroom, terwijl neurale synchronisatie juist extra voordelen biedt in situaties waarbij één ritmische stimulusstroom onderscheiden moet worden van afleidende stimuli. Daarom beschrijf ik in **hoofdstuk 5** een onderzoek waarin ik een intermodale selectieve aandachtstaak heb gebruikt met concurrerende auditieve en visuele stimuli. Hierbij richtte ik mij op het (i) repliceren van eerdere bevindingen van defecte motorische synchronisatie in patiënten in condities met één enkele stimulusstroom en (ii) het onderzoeken of een groter voordeel van synchronisatie, door het toevoegen van een afleidende stimulusstroom, zorgt voor motorische synchronisatie bij patiënten die anders niet wordt gezien. In tegenstelling tot deze hypothese, lieten Parkinson

patiënten in beide condities een verminderde motorische synchronisatie zien. Deze resultaten tonen aan dat motorische synchronisatie in patiënten defect is, zelfs in situaties die synchronisatie aanmoedigen.

Ter conclusie, de resultaten uit dit proefschrift bieden geen volledig beeld van de neurofysiologie van cueing bij de ziekte van Parkinson. Men zou zelfs kunnen zeggen dat er verschillende resultaten in staan die niet met elkaar te rijmen zijn. Aan de ene kant, een directe vergelijking tussen ritmische en niet-ritmische stimulatie liet gelijke effecten van ritmische stimulatie voor gezonde personen en patiënten. De gelijke vergroting van de beta-ERS fase, met een bijbehorende toename van anticiperende beta suppressie, wijst op een anticiperend gebruik van de cues in zowel patiënten als gezonde personen. Dit anticiperende gebruik van cues is een argument dat cueing afhankelijk is van interacties tussen de basale ganglia en de cortex, en deze interacties zelfs faciliteert. Deze kijk op cueing contrasteert met de populaire visie dat cueing vooral werkt omdat het alternatieve neurale gebieden aanspreekt.

Aan de andere kant zijn niet alle bevindingen uit dit proefschrift zo makkelijk in deze visie te passen. In de experimenten waarin deelnemers seriële motorische responsen gaven op series van stimuli, was de modulatiediepte van motorische (beta) activiteit gelijk tussen patiënten en gezonde personen. Echter, het algemene patroon van sterkteverandering in beta golven was bij patiënten veel reactiever van aard, met meer reactieve dan anticiperende beta suppressie. Hetzelfde geldt voor de experimenten waarin deelnemers aandachtig een serie van stimuli moeten volgen en af en toe moeten reageren op een target. Daarin lieten patiënten zeer weinig entrainment zien van motorische corticale activiteit, terwijl gezonde personen sterke fluctuaties in motorische gereedheid lieten zien, welke gesynchroniseerd was met het stimulusritme. Daarom moeten we ook concluderen dat, in patiënten, externe stimulatie niet leidt tot (generatie van) een intern ritme die de motorische gereedheid moduleert.

Ondanks dat de resultaten niet convergeren naar een simpele verklaring van het klinische voordeel van ritmische cues bij de ziekte van Parkinson, laat dit proefschrift wel het nut zien van neurofysiologische analyses van hersengolven om de neurale basis van entrainment te onderzoeken. Omgekeerd, het onderzoek naar ritmisch cueing bij Parkinson, waarvan het effect waarschijnlijk afhangt van entrainment, is een vruchtbare manier gebleken om neurofysiologische theorieën over de belangrijke rol van entrainment van hersengolven te testen, in zowel cognitief als motorisch gedrag.

Publications

A shift from prospective to reactive modulation of beta-band oscillations in Parkinson's disease
te Woerd E.S., Oostenveld R., de Lange F.P., Praamstra P. (2014)
Neuroimage, 100: 507-519

Rhythmic entrainment of slow brain activity preceding leg movements
Heideman S.G., **te Woerd E.S.**, Praamstra P. (2015)
Clinical Neurophysiology, 126: 348-355

Effects of rhythmic stimulus presentation on oscillatory brain activity: the physiology of cueing in Parkinson's disease
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Journal of Neurophysiology, 117: 1853-1864

Entrainment for attentional selection in Parkinson's disease
te Woerd E.S., Oostenveld R., de Lange F.P., Praamstra P. (2018)
Cortex, 99: 166-178

Curriculum Vitae

Erik te Woerd was born in Winterswijk on April 16th 1988. He grew up in Lichtenvoorde and obtained his high school diploma from the Scholengemeenschap Marianum in Groenlo (voorbereidend wetenschappelijk onderwijs, specialization Nature and Health) in 2006. Erik went on to study Biomedical Engineering at the University of Twente with a specialization in Human Function Technology, from which he obtained his Bachelor's degree in 2010. He continued with a master in Biomedical Engineering at the University of Twente, from which he graduated in December 2011. During this period, Erik was awarded a PhD-position at the Department of Neurology of the Radboud University Medical Centre Nijmegen and moved to Doetinchem. The work of this PhD-project was executed at the Donders Institute for Brain, Cognition and Behaviour in Nijmegen, under supervision of Peter Praamstra from the Radboud University Medical Centre Nijmegen, and Floris de Lange from the Radboud University Nijmegen. In 2018, Erik completed his doctoral studies. In addition to his research, Erik has been involved in supervising master students, and has been part of the MEG-lab team (2012-2016). As of June 2017 Erik has moved back to Lichtenvoorde and is currently working as a data analyst at Achmea in Apeldoorn.

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Gezien de hoeveelheid studies die plaatsvinden binnen het Donders, en dan heb ik het nog niet eens over de verscheidenheid van studies, is het ongelofelijk om te zien dat de TG dit allemaal mogelijk weet te maken. Jullie zijn onmisbaar en

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Het werken aan dit proefschrift was interessant en fascinerend, maar op momenten ook zwaar en frustrerend. Juist op die momenten was ik zo blij dat ik even van me af kon praten tegen jullie. Ik waardeerde het ook om het juist over allerlei zaken te hebben die totaal niets met dit proefschrift te maken hebben en meestal voelden jullie precies aan waar ik behoefte aan had. Dank voor alle steun, bier, toernooien, weekenden, geweldige avonden en eten, heel, heel veel eten met mijn beste vrienden, **Frank**, **Koen**, **Remco** en **Tijs**. Logischerwijs ook dank aan **Bernice**, **Thomas**, **Jasper**, **Malou**, **Merel**, **Joep** en alle andere **vrienden** en **vriendinnen**! Dank voor al jullie (wellicht onbewuste) steun, het heeft me meer geholpen dan jullie denken.

Toen ik eind 2011 op zoek ging naar een promotieplek had ik niet veel eisen. Eigenlijk was de enige belangrijke eis dat het een patiëntenstudie moest zijn. Hoewel ik gedurende de jaren heb geleerd dat dit soort studies niet de makkelijkste onderzoeken zijn, denk ik nog steeds dat ze het meest interessant zijn. Naast de standaard onderzoeksvragen en methoden komen er namelijk zoveel meer zaken bij kijken: medicatieonthouding, parkeerplekken op loopafstand en uitvoerbaarheid van het experiment zijn maar een paar extra zaken waar je rekening mee moet

houden. De ontmoetingen met patiënten waren erg bijzonder en hun verhalen over dagelijkse problemen des te meer. Jullie moeite en bereidheid om deel te nemen aan deze onderzoeken, ondanks dat ze soms zeer confronterend waren vanwege de medicatieonthouding, zijn ontzettend waardevol voor de wetenschap. Daarom mijn enorme dank aan **alle patiënten en controles** voor hun deelname aan de verschillende studies in dit proefschrift.

Gedurende de zes jaar waarin ik aan dit proefschrift heb gewerkt, heb ik altijd de druk gevoeld dat ik alles op tijd af moest ronden. Hoewel iedereen zijn eigen manier vindt om om te gaan met deze druk, de stress en allerlei andere problemen die je tijdens je promotietraject tegenkomt, brengt het naderen van het einde van je contract andere vragen met zich mee. Wil ik verder in de wetenschap? Zo ja, waar en welk onderwerp? Zo nee, wat ga ik dan doen? Ik prijs mezelf gelukkig dat ik zo snel de ideale vacature vond, omdat het zoveel extra zorgen wegnam. Ik wil jullie, **Raymond** en **Tijmen** ook heel erg bedanken voor de vrijheid die ik kreeg om dit proefschrift af te kunnen ronden. **René**, **Maarten**, **Kelly**, **Pieter**, **Robert**, **Louis**, **Hans**, **Roland**, **Louise** en **de andere collega's**, dank voor al jullie interesse, koffie, begrip en het aanhoren van al mijn geklaag en slechte (of toch goede?) grappen.

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voor jou, **Marleen**.

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